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President:
Pier Luigi Zinzani

Monoclonal B- cell Lymphocytosis(MBL): low vs high count

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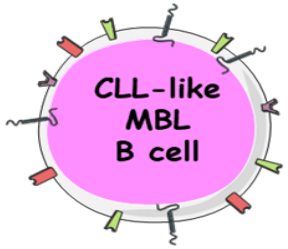
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Astra Zeneca					X		
Amgen					X		
BluePrint Medicines	X				X	X	
Janssen					X		
Becton/Dickinson					X	X	X
ImmunoStep SL						X	X
300 K Biotech Solutions						X	X

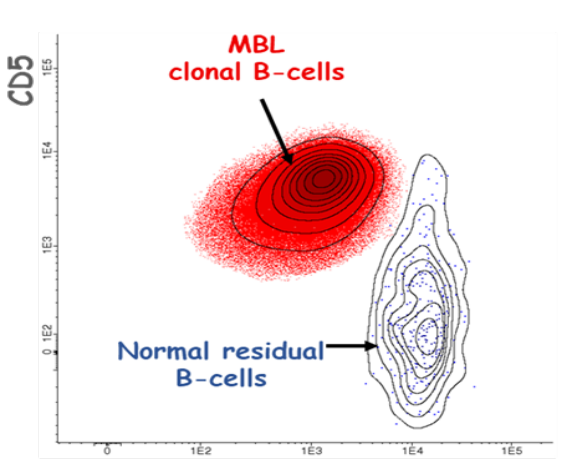
MONOCLONAL B CELL LYMPHOCYTOSIS (MBL)

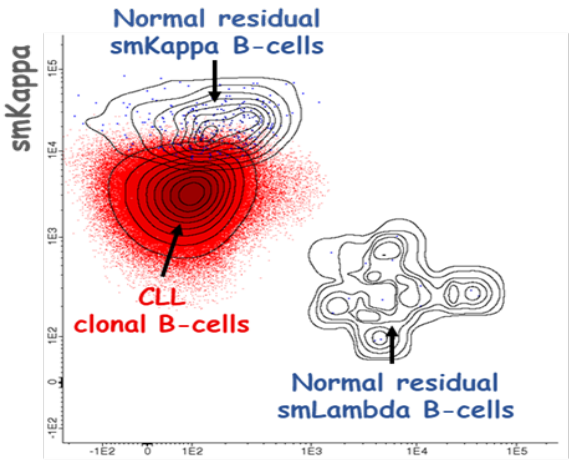
- Monoclonal B-cell Lymphocytosis (MBL) indicates the presence of <5x10^9 clonal B-cells/L in PB of otherwise healthy subjects, with or without lymphocytosis (ICD-O Codes: 9823/1 for CLL type MBL and 9591/1 for Non-CLL type MBL)

	PacB	OC515	FITC	PE	PerCPCy5.5	PECy7	APC	APCH7
LST® Tube	CD20+CD4	CD45	CD8+sIgλ	CD56+sIgκ	CD5	CD19+TCRγδ	CD3	CD38
Characterization Tube	CD20	CD27	CD5	LAIR-1	CD79b	CD19	CD3+sIgκ	sIgλ



CD19$^+$
CD20^{lo}
CD79b^{lo}
CD5$^+$
CD27$^+$
CD23$^+$
CD200^{hi}





Typical CLL-like CD5$^+$:
-CD20^{lo},CD79^{lo},sIg^{lo}

Atypical CLL-like CD5$^+$:
-CD20^{hi} or CD79^{hi} or sIg^{hi}

Non-CLL-like CD5$^-$

Marti et al, Br J Haematol 2005, 130: 325-32; Swerdlow et al, Blood 2016, 127: 2375-90

MONOCLONAL B CELL LYMPHOCYTOSIS (MBL): SUBTYPES

WHO 2022 Classification of MBL

Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	(Same)
(Entity deleted)	B-cell prolymphocytic leukaemia

Pre-neoplastic and neoplastic small lymphocytic proliferations: MBL and CLL/SLL remain; B-PLL is no longer recognized as an entity

This family comprises two entities: Monoclonal B-cell Lymphocytosis (MBL) and Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL). WHO-HAEM5 recognizes three subtypes of **monoclonal B-cell lymphocytosis (MBL)**:

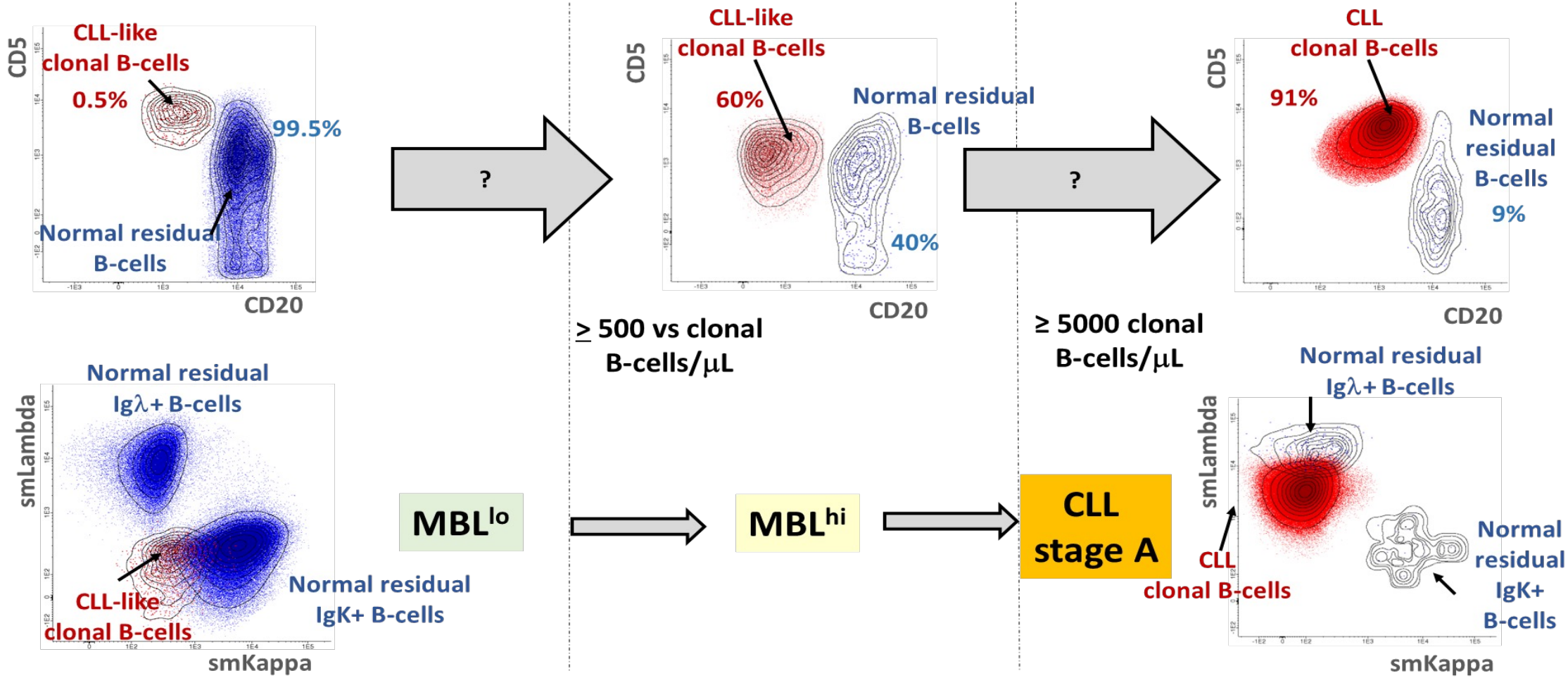
a. **Low-count MBL or clonal B-cell expansion**: clonal CLL/SLL-phenotype B-cell count below 0.5×10^9/L with no other features diagnostic of B-lymphoproliferative disorder. The arbitrary threshold is based on the distribution of clonal B-cell counts in population studies compared to clinical cohorts [29].

b. **CLL/SLL-type MBL:** monoclonal CLL/SLL-phenotype B-cell count $\geq 0.5 \times 10^9$/L and total B-cell count less than 5×10^9/L with no other features diagnostic of CLL/SLL [30]. The threshold of less than 5×10^9/L is arbitrary but identifies a group with a very low likelihood of requiring treatment compared to individuals with B-cell counts between 5–10 x 10^9/L [31].

c. **non-CLL/SLL-type MBL:** ANY monoclonal non-CLL/SLL phenotype B-cell expansion with no symptoms or features diagnostic of another mature B-cell neoplasm. The majority of cases have features consistent with a marginal zone (MZ) origin [32].

Alaggio et al, Leukemia 2022, 36: 1720-48

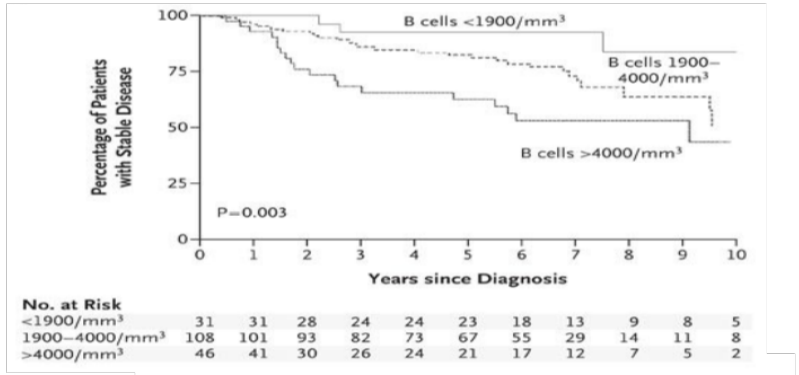
CLASSIFICATION OF MBL^{lo} vs MBL^{hi} vs STAGE A CLL relies on clonal B-cell counts

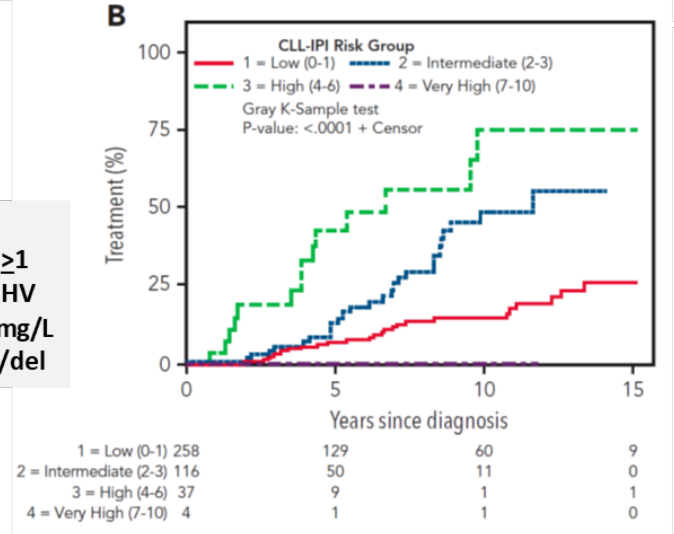


Population-based (flow cytometry) studies

Routine-blood (lymphocyte) count at primary vs hospital health care

MBL^{hi} clones with higher mutational load show shorter time to therapy (TTT)





- Age >65y
- RAI stage ≥1
- Unmut-IGHV
- β2M>3.5mg/L
- TP53 mut/del

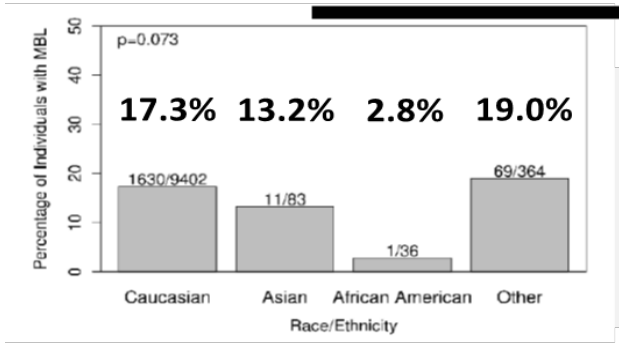
	MBL^{hi} (N=112)					
	Total		Event			
Mutated genes	N	%	N	HR	95% CI	P
None	51	45.5	3	1	reference	
Any	**61**	**54.5**	**17**	**3.77**	**(1.09-13.0)**	**0.035**
0	51	45.5	3	1	reference	
1	34	30.4	7	3.09	(0.78-12.2)	0.11
2+	**27**	**24.1**	**10**	**4.42**	**(1.20-16.3)**	**0.026**
Cont.	112		20	1.47	(1.11-1.96)	0.008
c-statistic				0.72	(0.60-0.84)	

Rawstron et al, N Eng J Med, 2008, 359: 575-82; Parikh et al, Blood 2021, 138: 149-59

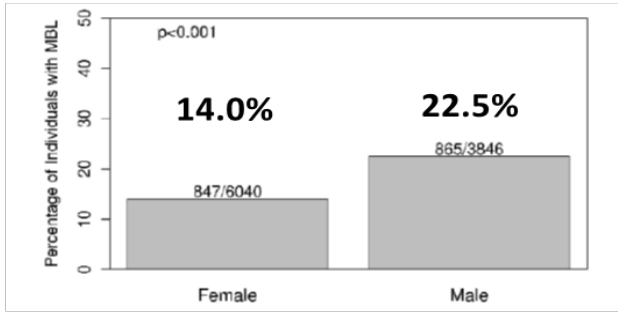
Kleinstern et al, Am J Hematol, 2020; 95: 906-17 (Suppl material)

PREVALENCE OF MBL IN THE GENERAL POPULATION*

	Europe/USA	Japanese (living in Brazil)	UAE	Uganda	Mexico
MBL^{lo}:	3.5%-17%	7.7%-10%	5.8%	14%	9.4%
CLL-like	85%**	100%	48%	3%	NA
Non-CLL	15%	0%	52%	97%	NA



- MBL in relatives of sporadic CLL patients: 5%-14%
- MBL in relatives of familial CLL patients: 14%-18%
- MBL in patients with lymphocytosis: 3%-14%

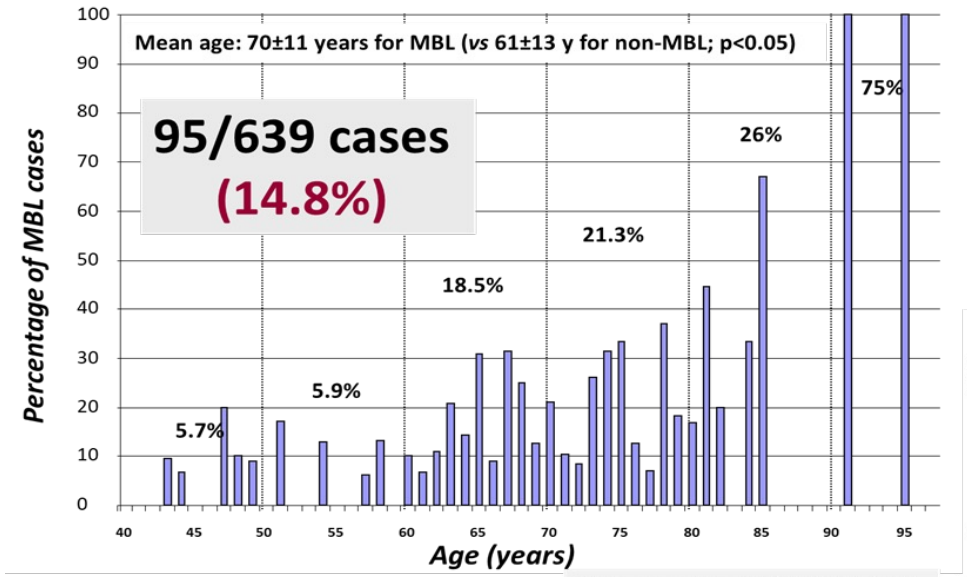


MBL^{lo}: 245/1094 (22%) vs MBL^{hi}: 22/1094 (2%) vs CLL: 2/1094 (0.18%)

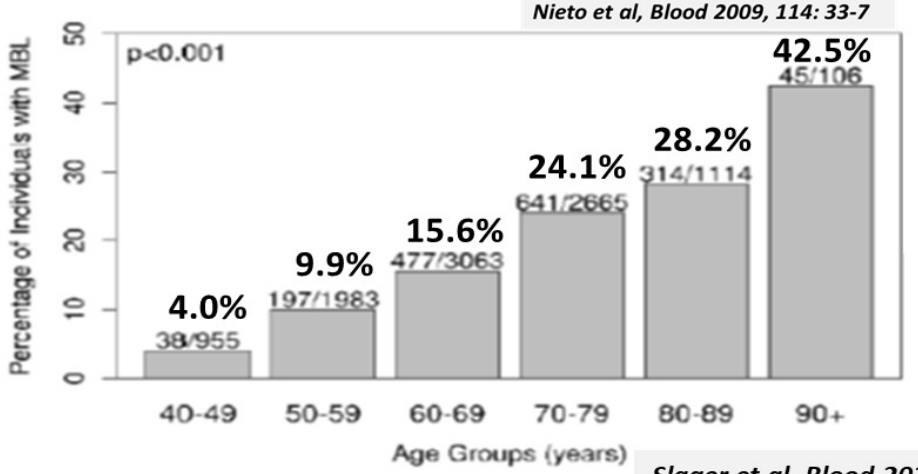
*Two hospital-based studies on adults with lymphocytosis in China -n=14/254 (5.5%); 4/14 CLL (1.6%) and 10/14 (3.9%) MBL: 2/10 (20%) CLL-like MBL- and South Korea -3/105 (2.9%): 2/3 (67%) CLL-like MBL-; ** similar distribution in tissue (53 LN, spleen) as described by Habermehl et al, Pathol Arch Lab Med 2020.

Rawstron et al, Blood 2002; Ghia et al, Blood, 2004; Rachel et al, Br J Hematol, 2007; Nieto et al, Blood, 2009; Shim et al, Blood 2014; Rawstron et al, Lancet Hematol, 2017; Rodriguez-Preciado et al, Int J Immunogen, 2017; Faria-Moss et al Haematologica 2020; Xu et al, BMJ Open, 2020; Yoo et al, Ann Lab Med 2020; Slager et al, Blood 2022

Frequency of MBL in blood of (healthy) adults



Nieto et al, Blood 2009, 114: 33-7

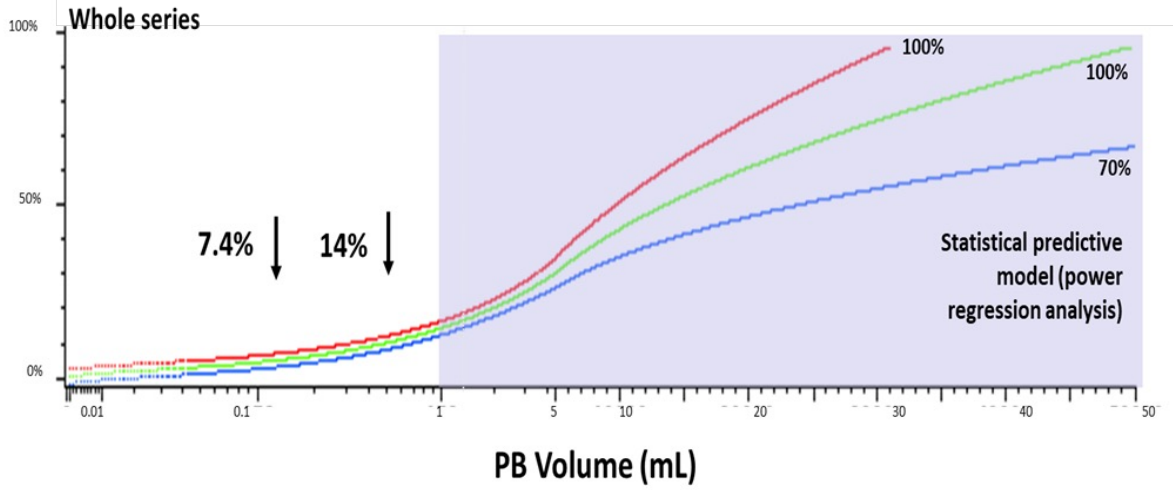


Slager et al, Blood 2022

% of cases with CLL-like B-cell clones

FREQUENCY DETECTED

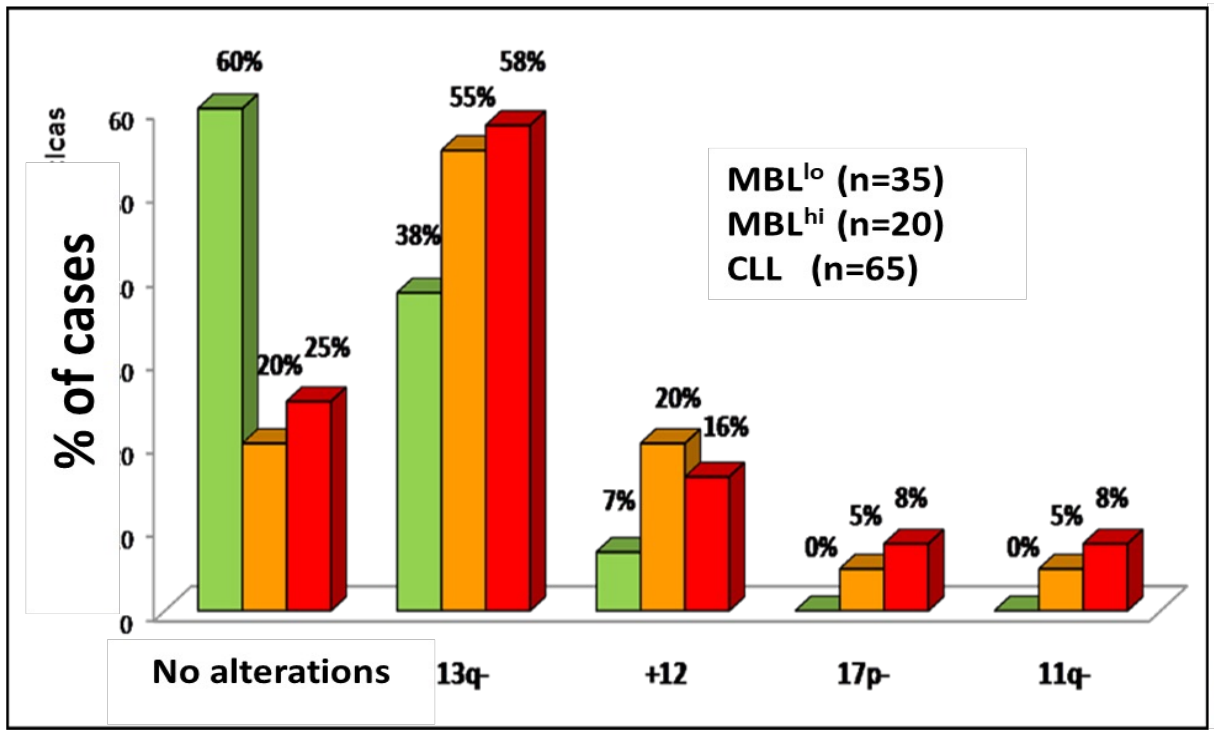
CALCULATED FREQUENCY



Acquisition of data on >10^7 blood leucocytes for sensitive detection of MBL^{lo} recommended

Almeida et al, Leukemia 2011, 25: 718-22

Cytogenetic profile of CLL-like MBL^{lo} vs MBL^{hi} vs CLL



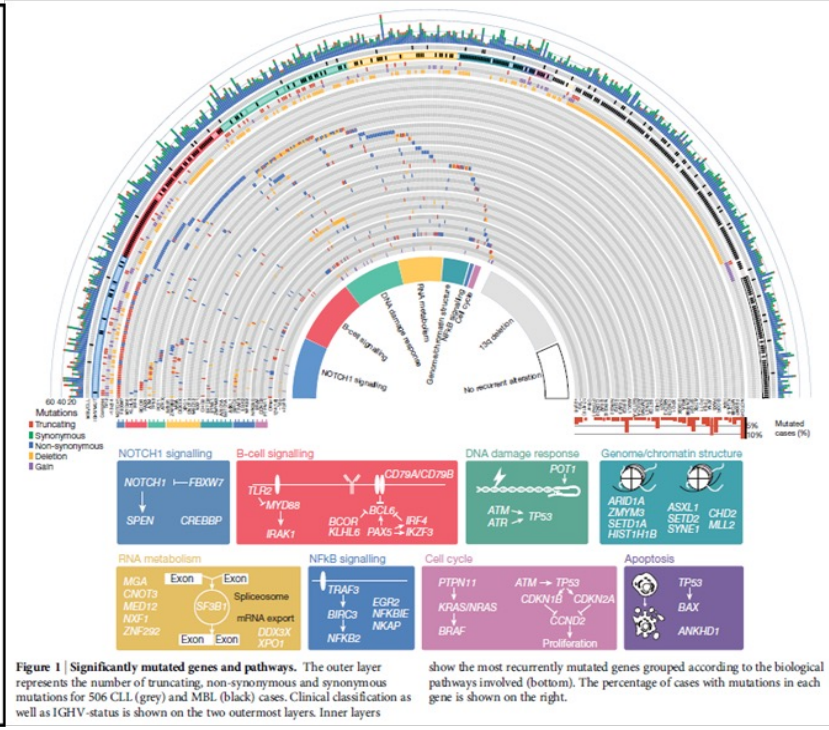


Figure 1 | Significantly mutated genes and pathways. The outer layer represents the number of truncating, non-synonymous and synonymous mutations for 506 CLL (grey) and MBL (black) cases. Clinical classification as well as IGHV-status is shown on the two outermost layers. Inner layers show the most recurrently mutated genes grouped according to the biological pathways involved (bottom). The percentage of cases with mutations in each gene is shown on the right.

Driver genes in CLL vs MBL^{hi}

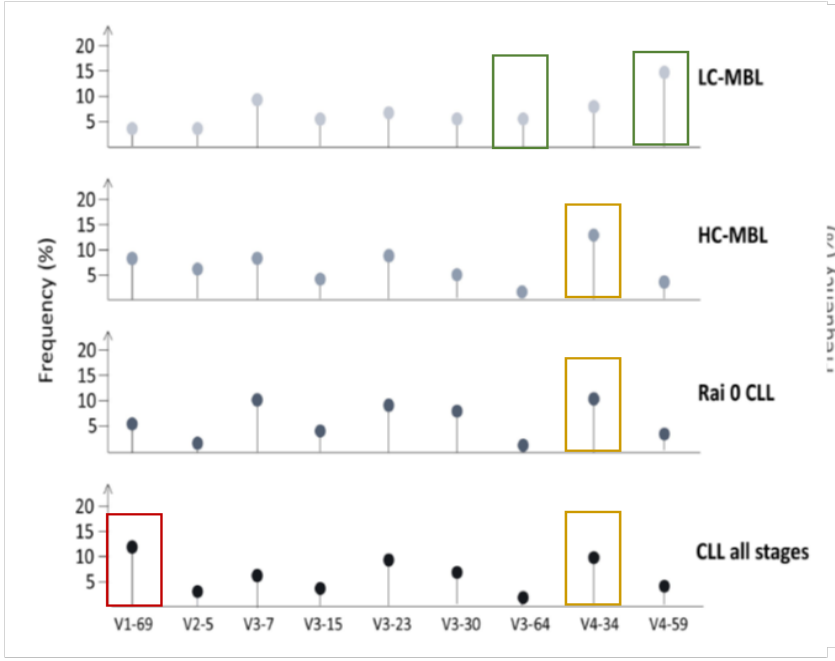
	CLL (N=445)		HC MBL (N=112)	
Gene	N	%	N	%
NOTCH1	69	15.5%	7	6.2%
SF3B1	56	12.6%	14	12.4%
TP53	43	9.7%	7	6.2%
NFKBIE	39	8.8%	3	2.7%
ATM	35	7.9%	3	2.7%
XPO1	31	7.0%	1	0.9%
BIRC3	30	6.7%	7	6.2%
CHD2	22	4.9%	5	4.4%
MED12	22	4.9%	2	1.8%
MYD88	20	4.5%	8	7.1%
MGA	19	4.3%	1	0.9%
BRAF	18	4.0%	1	0.9%
EGR2	18	4.0%	3	2.7%
KRAS	18	4.0%	2	1.8%
ZNF292	15	3.4%	1	0.9%
DDX3X	14	3.1%	4	3.5%
ASXL1	13	2.9%	.	.
BAZ2A	13	2.9%	2	1.8%
BCOR	13	2.9%	.	.
FBXW7	13	2.9%	4	3.5%
RPS15	13	2.9%	.	.
FUBP1	12	2.7%	.	.
KMT2D	7	1.6%	.	.
ZMYM3	7	1.6%	2	1.8%
BRCC3	6	1.3%	1	0.9%
NRAS	6	1.3%	.	.
NXF1	6	1.3%	.	.
POT1	6	1.3%	1	0.9%
SETD2	6	1.3%	1	0.9%
CHEK2	5	1.1%	.	.
ITPKB	4	0.9%	2	1.8%
ARID1A	3	0.7%	1	0.9%
CREBBP	3	0.7%	1	0.9%
SAMHD1	3	0.7%	.	.
TRAF3	3	0.7%	.	.
ELF4	2	0.4%	.	.
EWSR1	2	0.4%	.	.
SYNE1	2	0.4%	.	.
TRAF2	2	0.4%	.	.
CNOT3	1	0.2%	2	1.8%
KLHL6	1	0.2%	1	0.9%
SETD1A	1	0.2%	.	.
XPO4	1	0.2%	.	.
ATRX	.	.	.	.
CARD11	.	.	.	.
CCND2	.	.	.	.
DYRK1A	.	.	.	.
FAM50A	.	.	.	.
GNB1	.	.	.	.
HIST1H1B	.	.	.	.
HIST1H1E	.	.	.	.
IKZF3	.	.	.	.
IRF4	.	.	.	.
MAP2K1	.	.	.	.
NFKB2	.	.	.	.
PAX5	.	.	.	.
PTPN11	.	.	.	.
RIPK1	.	.	.	.
BTK	.	.	.	.

The genetic/molecular profile of clonal B-cells in MBL^{lo} and MBL^{hi} overlaps with that of overt CLL in the absence of a (single) common genetic driver

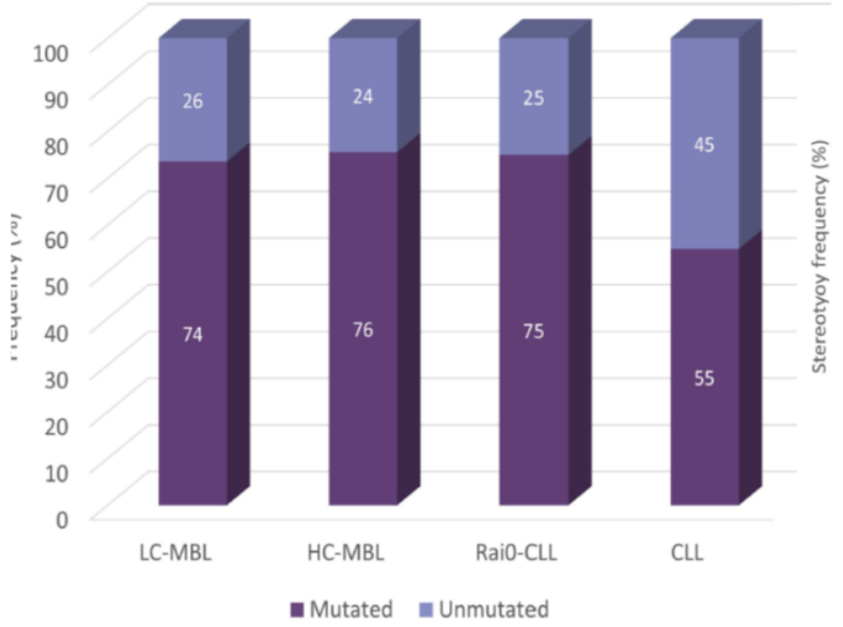
Nieto et al Blood 2009 114: 33-7; Criado et al, Haematologica 2018, 103: 1198-208; Kleinstern et al, Am J Hematol 2020, 95: 906-017; Puente et al, Nature 2015, 526: 519-24

ONTOGENY OF MBL AND CLL: role of BCR (signaling)

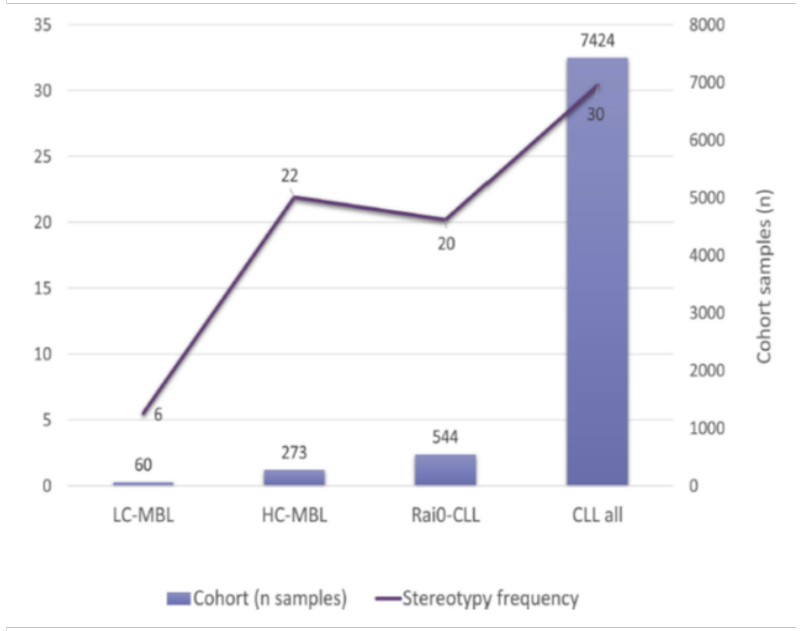
IGHV repertoire in MBL vs CLL



IGHV mutational status in MBL vs CLL



BcR IG stereotypes in MBL vs CLL

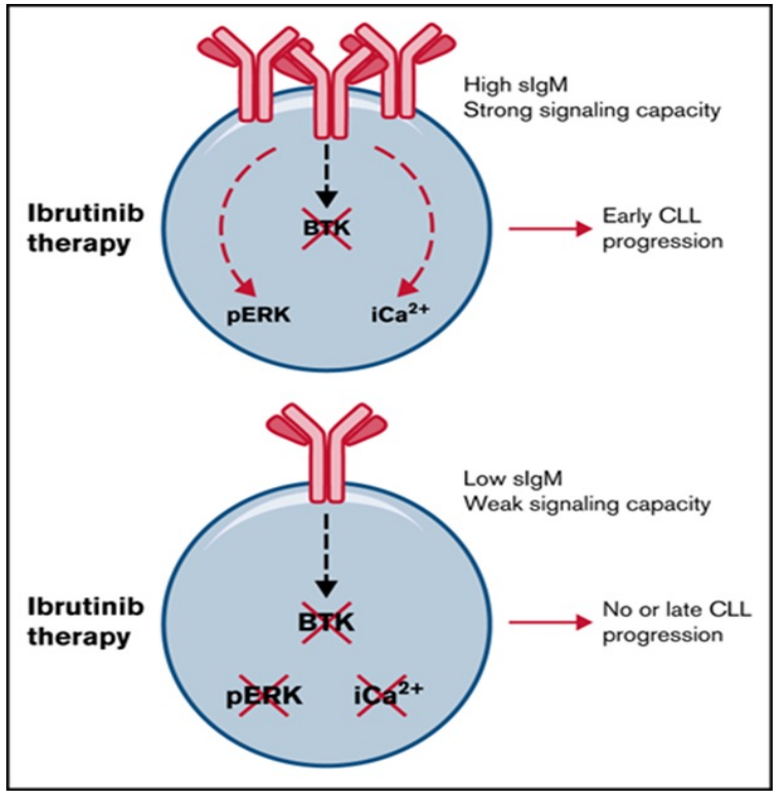


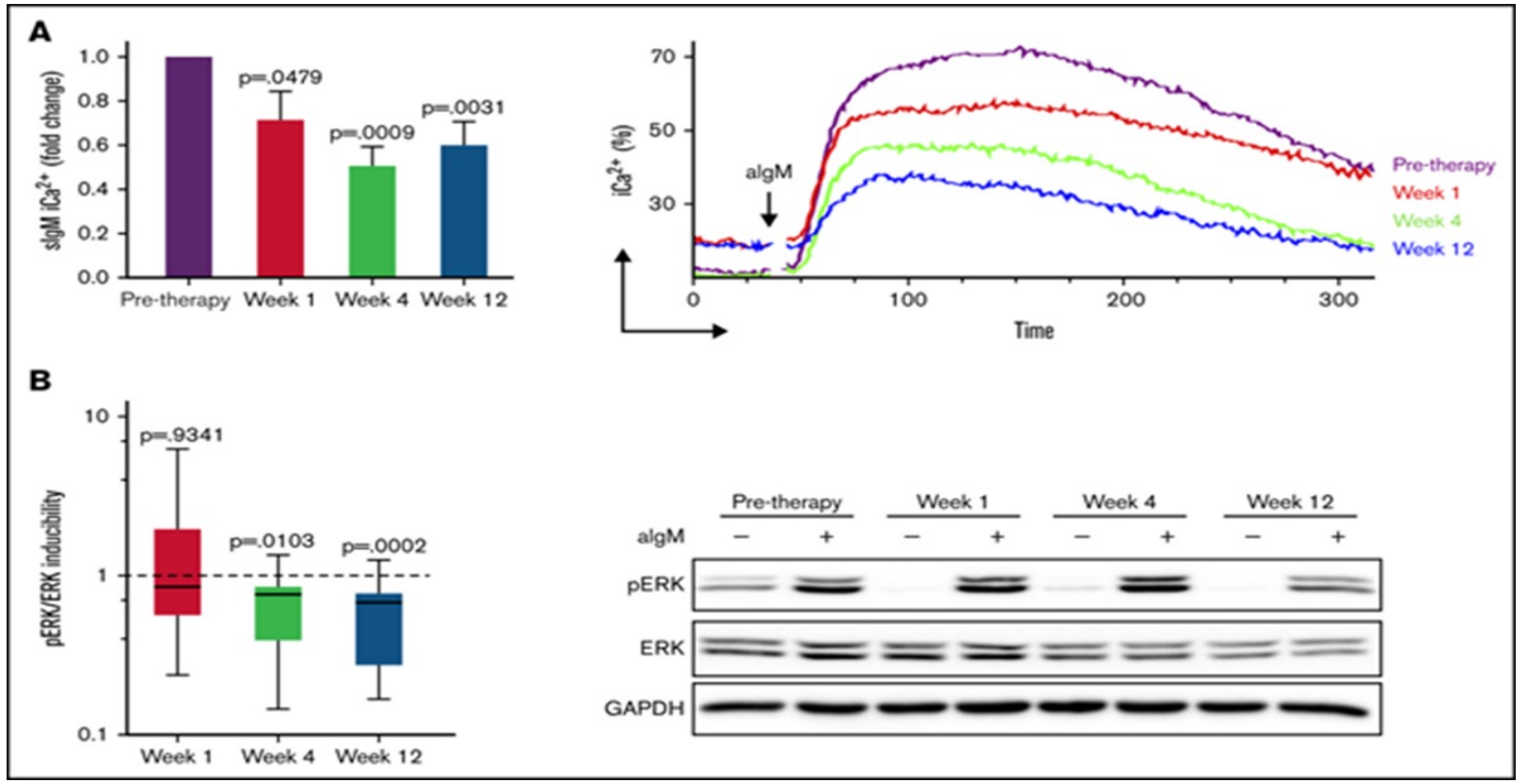
The frequency of cases with ≥ 2 B-cell clones decreases from MBL^{lo} (12%-19%) to MBL^{hi} (2.9%-13%) and CLL patients (0.7%-3.5%)

Vardi et al, Blood 2013, 121: 4521-5; Galigalidou et al, Front Oncol 2021, 11: e769612; Faria Moss et al, Haematologica 2020,105: e298-301.

ONTOGENY OF MBL AND CLL: role of BCR and not TLR (signaling) in CLL

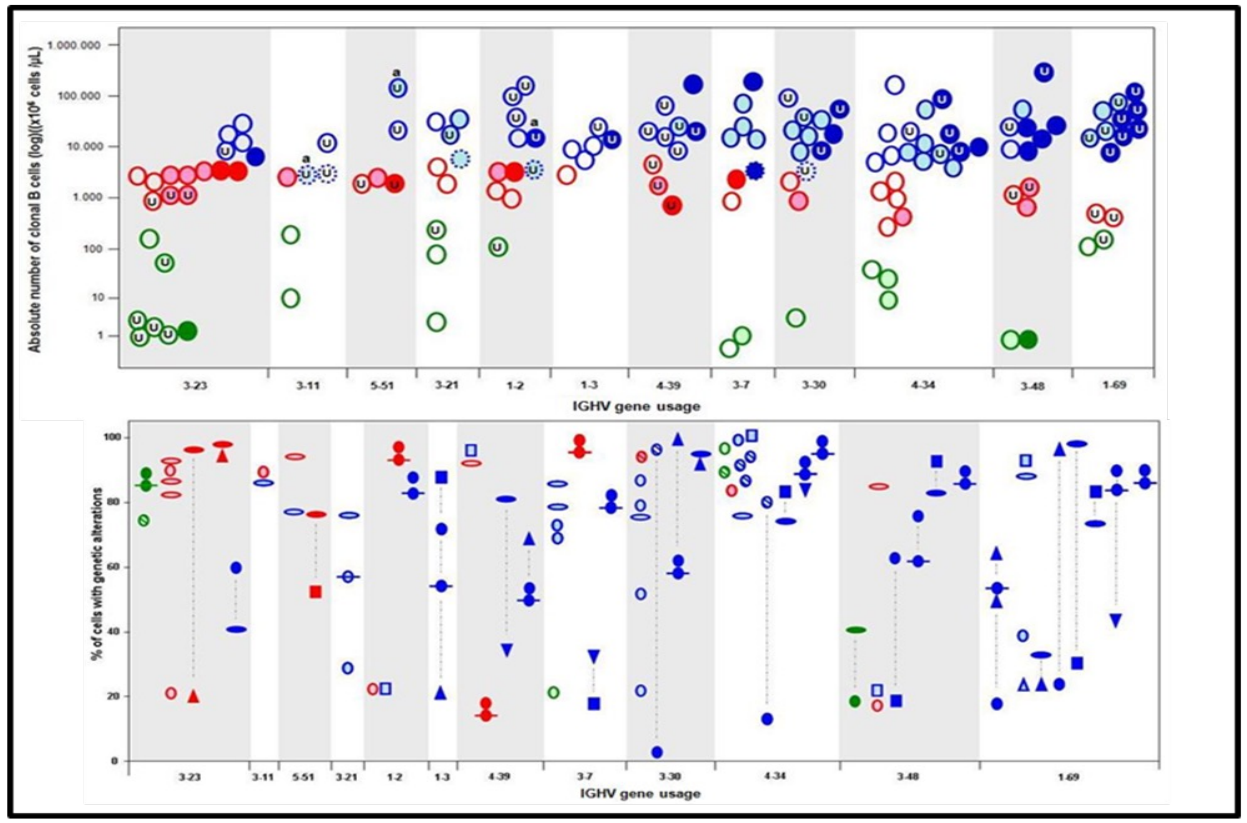
Higher expression of SIgM translates into higher BCR signaling and lower BTK

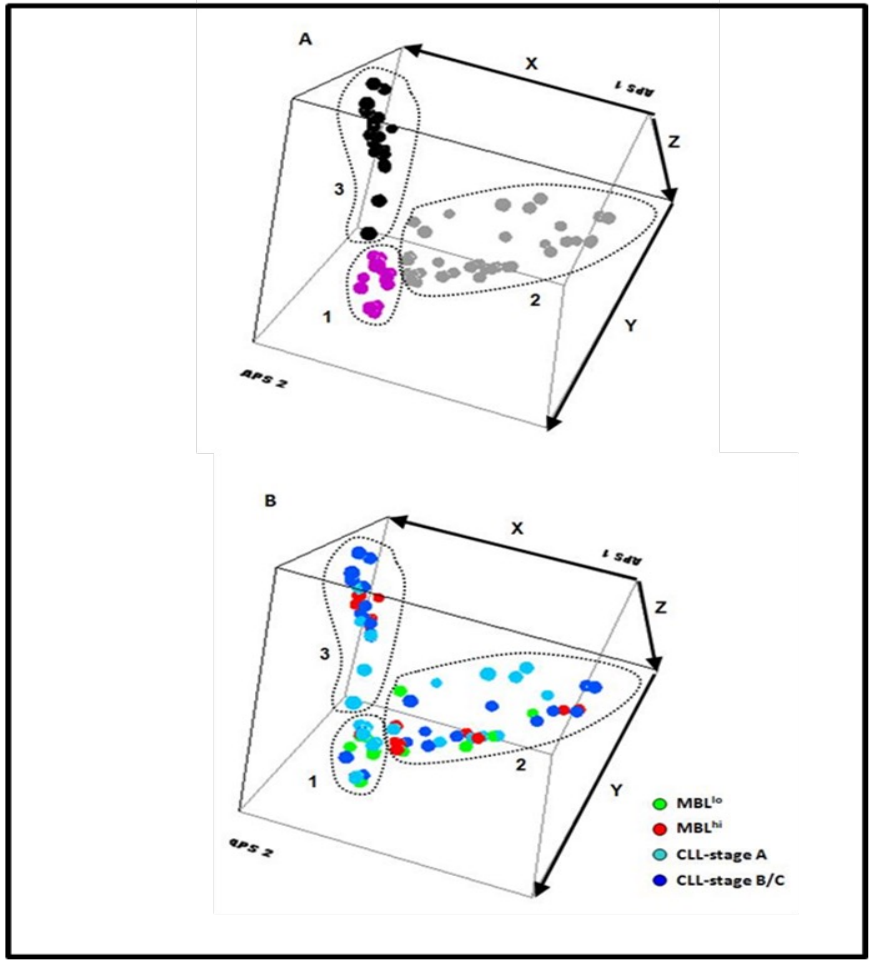




Chiodin et al, Blood Adv 2022, 6: 5494-504; Martines et al, Blood 2022, 140: 2335-47

Immunogenotypic and molecular/cytogenetic patterns of MBL^{lo} vs MBL^{hi} vs CLL



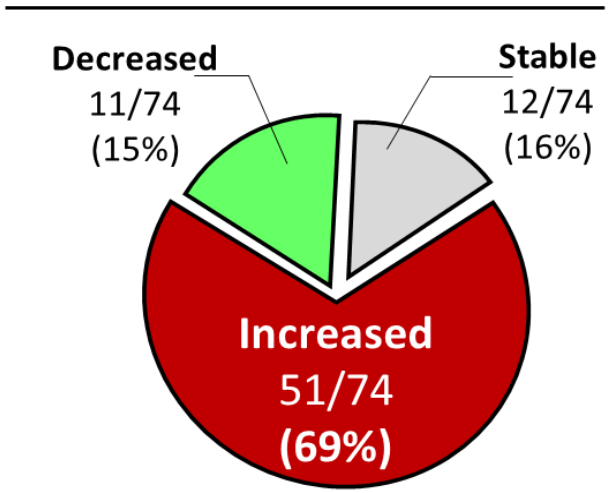


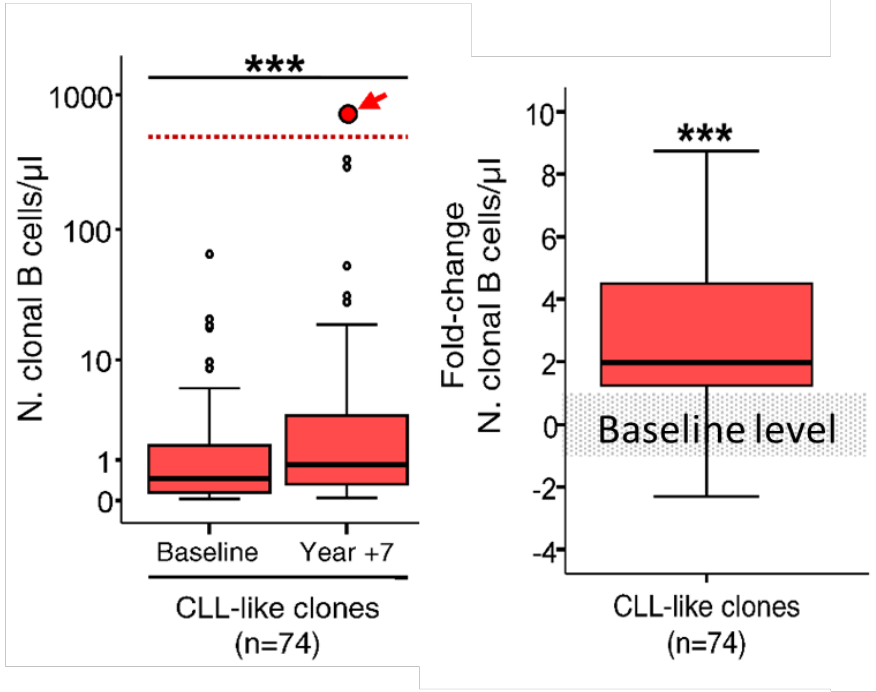
There is a significant association between the IGHV repertoire and the cytogenetic/molecular profiles of clonal B-cells in the different entities

Henriques et al, PlosONE 2013

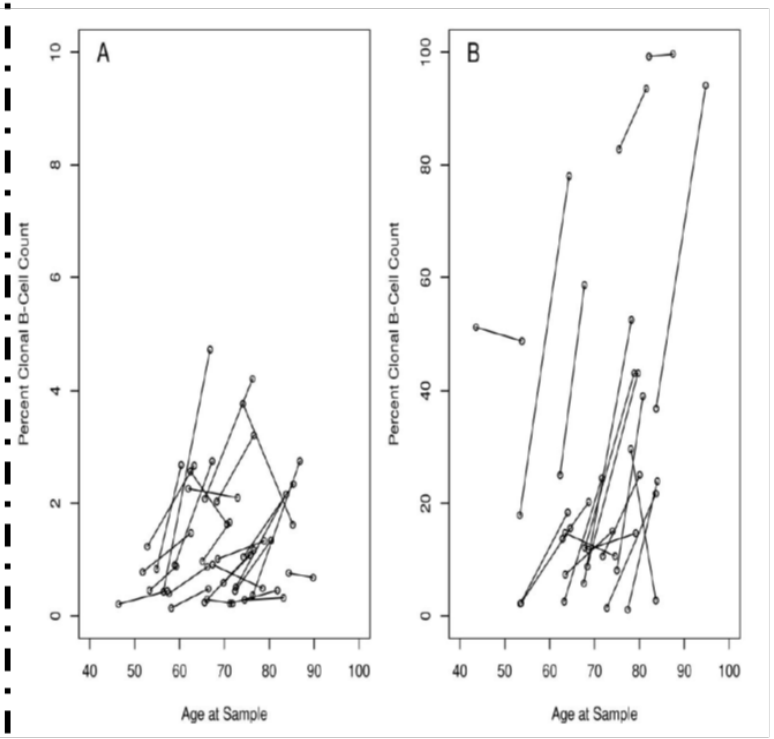
Low-count MBL persists after 7 years of follow-up

In 74/74 MBL^{lo} CLL-like clones persisted over time





Criado et al, Haematologica, 2018 103: 1198-208



Slager et al, Blood, 2022

In MBL^{lo} CLL-like clones persisted over time and double their numbers after 7y of follow-up with a very low rate (1-2% at 7 years follow-up) of progression to MBL^{hi} and to CLL (<0.1% per year)

Purroy et al, Blood, 2022: 139: 2252-4

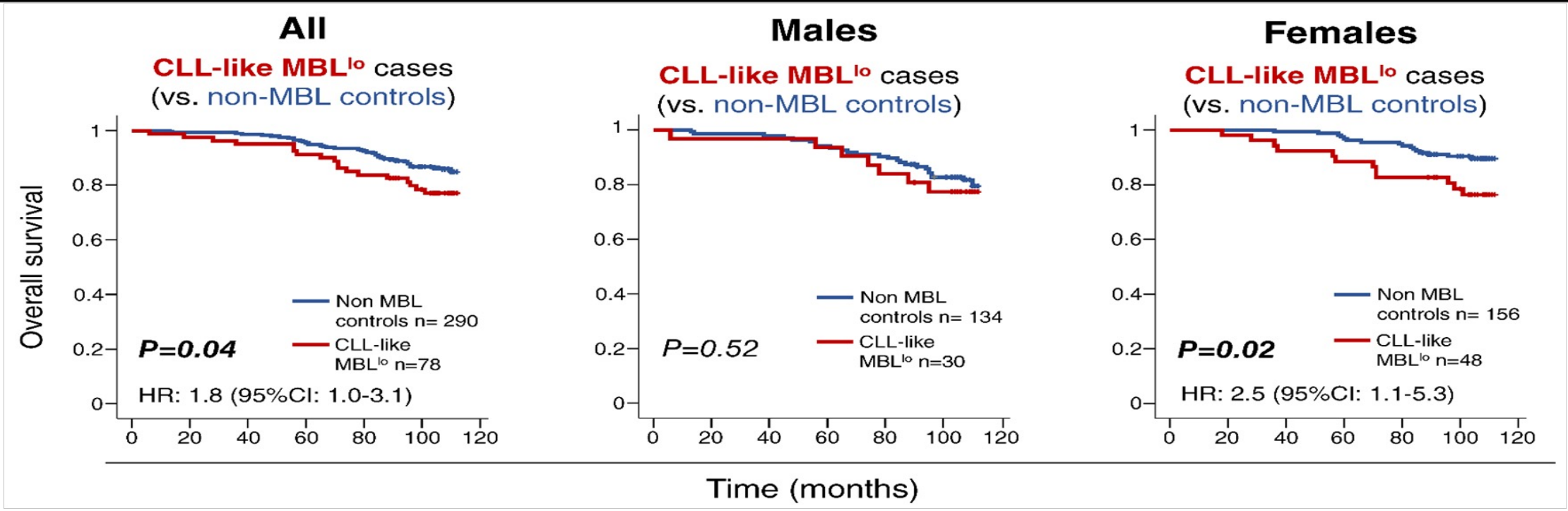
CLL-like MBL^{lo} clones acquire additional cytogenetic alterations after 7 years of follow-up

ALL CLL-like MBL^{lo} CASES	BASELINE	7y FOLLOW-UP	P-value
Altered/total cases (%)	**7/24** (29%)	**31/50** (62%)	0.01
del13q14(*D13S25*)	**6/20** (30%)	**27/48** (56%)	0.06
Trisomy 12	1/19 (5.3%)	1/49 (2%)	NS
del11q(*ATM*)	0/10 (0%)	0/48 (0%)	NA
del17p(*TP53*)	0/8 (0%)	1/48 (2.1%)	NS
del/t14q32	NA	5/23 (22%)	NA

PAIRED CLL-like MBL^{lo} SAMPLES	BASELINE	7y FOLLOW-UP	P-value
del13q14(*D13S25*)	**4/14** (29%)	**8/14** (57%)	0.04
Trisomy 12	1/13 (7.7%)	1/13 (7.7%)	NS
del11q(*ATM*)	0/8 (0%)	0/8 (0%)	NA
del17p(*TP53*)	0/7 (0%)	0/7 (0%)	NS

Criado et al, Haematologica, 2018; 103: 1198-208

MBL^{lo} in healthy subjects is associated with shorter survival



No significant differences in OS at 3y
Lamb et al, BMJ Open, 2021; 11: e041296

	Cardiovascular disease	Cancer#	Infection	Other#
CLL-like MBL^{lo}	29%	36%	21%	14%
General population*	33%	26%	1.4%	39.6%

*Data obtained from INE databases.
#Infection was the direct cause of death in one individual in these groups.

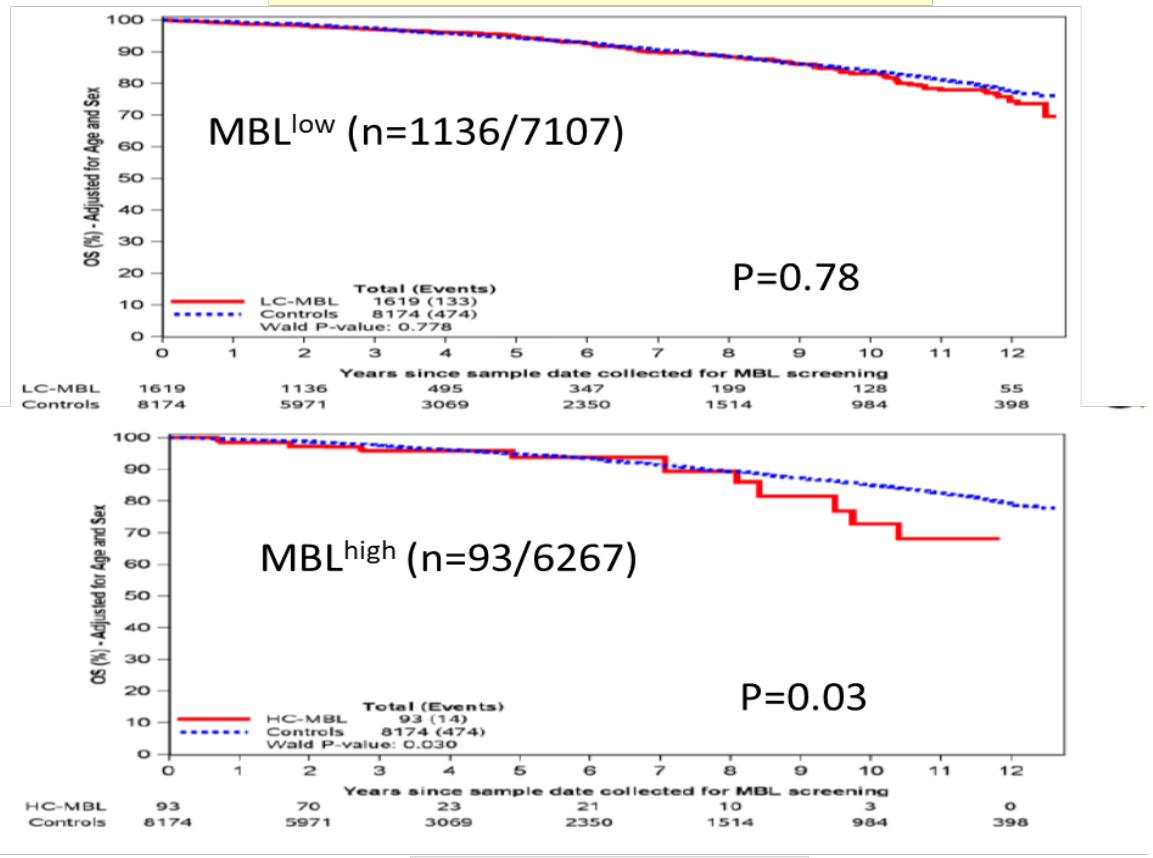
Criado et al, Haematologica, 2018; 103: 1198-208

Impact of low-count MBL on outcome in the general population: multivariate and confirmatory analyses

Variables	HR (95%CI)	P-value
Whole cohort (men plus women)		
Cardiovascular disease	2.65 (1.30 - 5.41)	0.007
Age (<65y vs. ≥65y)	5.08 (1.48 - 17.49)	0.01
Solid tumor	2.86 (1.26 - 6.46)	0.01
MBL^{lo} clones	2.14 (0.97 - 4.72)	0.06
Men		
Cardiovascular disease	4.43 (1.41 - 13.91)	0.01
Women		
Hypertension	6.84 (1.51 - 30.93)	0.01
Cardiovascular disease	5.95 (1.35 - 26.19)	0.02
MBL^{lo} clones	6.50 (1.34 - 31.49)	0.02
Solid tumor	10.82 (1.44 - 81.42)	0.02
N. of PB monocytes (/µL)	1.01 (1.00 - 1.01)	0.04
Diabetes	5.17 (0.89 - 29.92)	0.07
Severe infections	3.79 (0.88 - 16.27)	0.07

Criado et al, Haematologica, 2018; 103: 1198-208

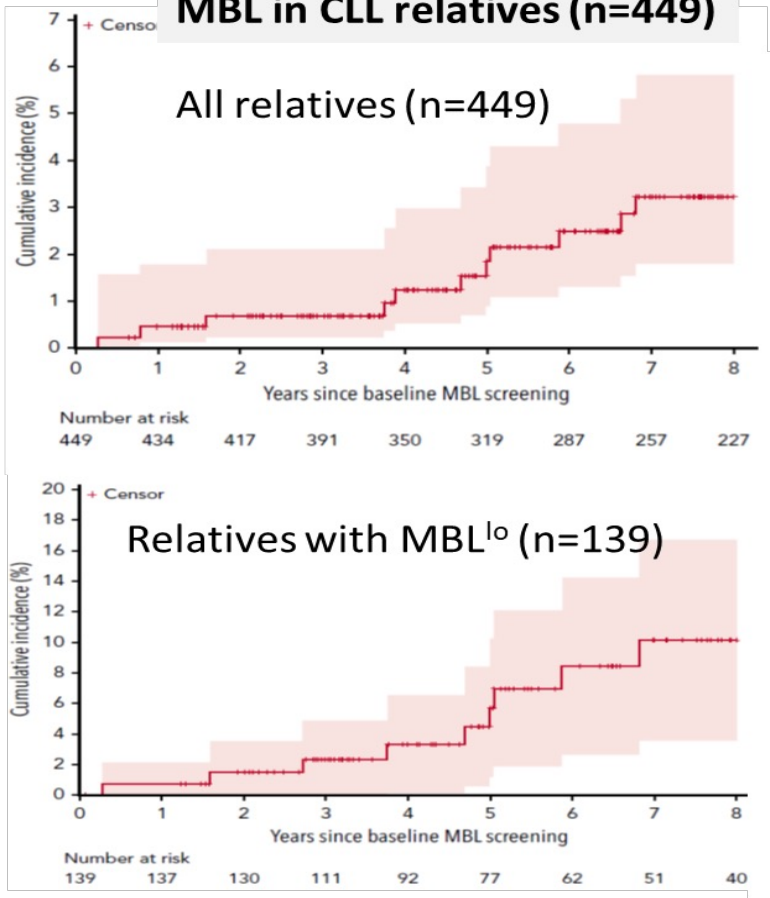
No significant differences in OS at 3y
Lamb et al, BMJ Open, 2021; 11: e041296



Slager et al, Blood, 2022

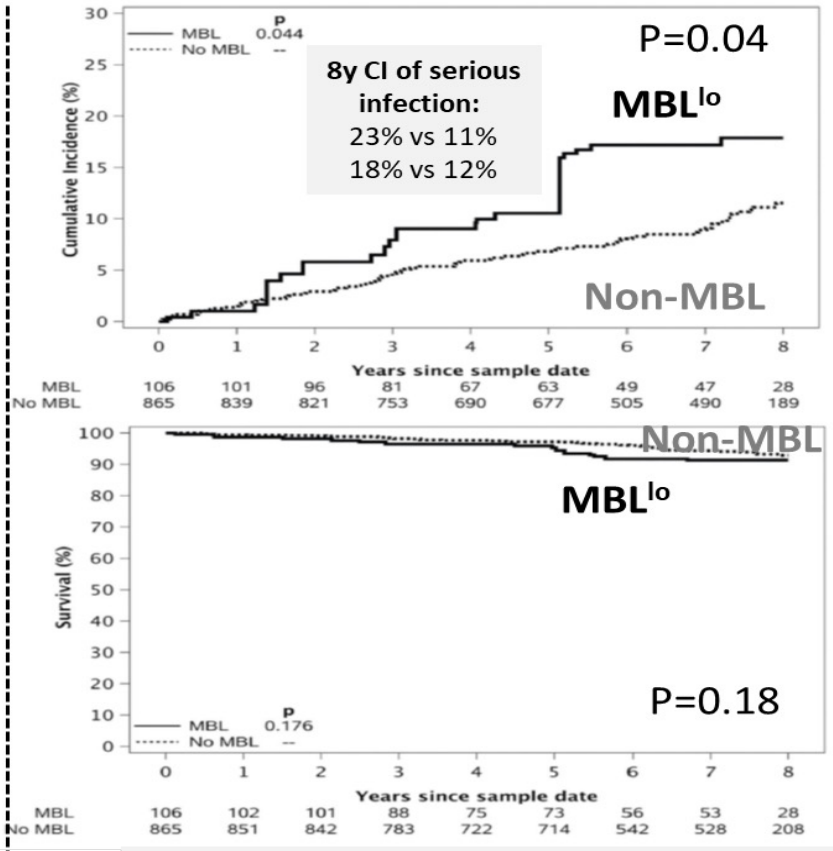
MBL^{lo} in a screening population and CLL relatives: progression to CLL

MBL in CLL relatives (n=449)

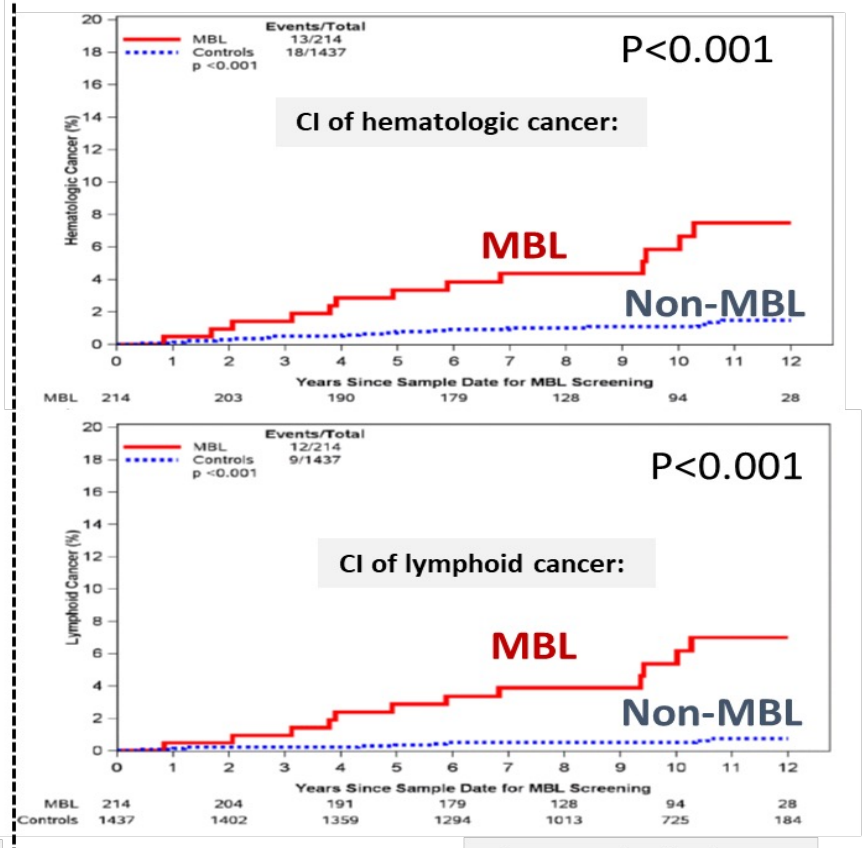


Slager et al, Blood, 2021; 137: 2046-56

MBL in the general population (n=449)



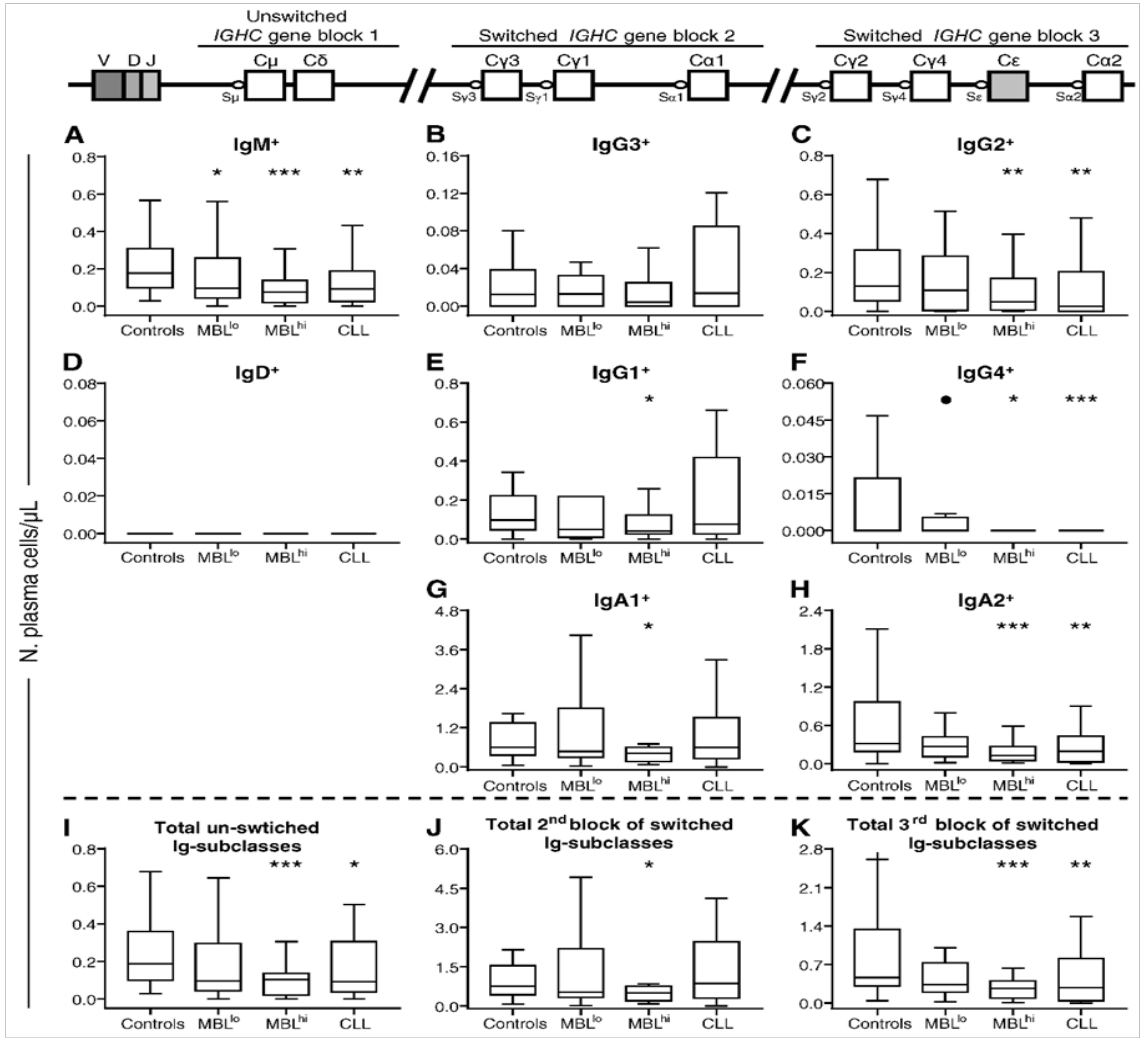
Shanafelt et al, Leukemia, 2021; 35: 239-44



Slager et al, Blood, 2022

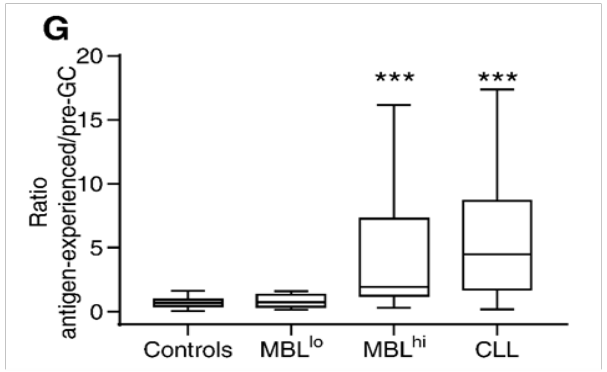
MBL^{lo} among relatives of familial CLL patients show higher rates of progression to CLL (5.7% at 5 years follow-up), severe infections and hematologic (lymphoid) cancer

Progressively altered B cell and plasma cell subsets from MBL to CLL



*P-value <0.05, ** P-value <0.01, ***P-value ≤0.001 vs. Controls

Decreased B-cell production
with a potentially
narrower B-cell repertoire



Sequential decrease in:

i) IgM+ PC in MBL^{lo},
ii) all PC subsets in MBL^{hi},
iii) but only IgG$_{2+4}$, IgA$_2$ in stage A CLL

Criado et al, Leukemia 2108, 32: 2701-5

SEROLOGIC RESPONSE TO VACCINATION IN MBL + CLL

VACCINE TYPE		DATE	CONTROLS	MBL^{hi}	CLL
Influenza vaccine:	A/H1N1	Day +28	98.8%	69.2%	58.8%
	A/H3N2	Day +28	98.6%	100%	83.3%
	B	Day +28	86.2%	76.9%	17.6%
Herpes zoster (R) vaccine		Month +3	63%	51%	36%*
SARS-CoV-2 vaccine 1st dose		Week +2-4	NR	50.0%	21.8%
(AZ, Mod, Pfizer)	2nddose	Week +2-4	NR	90.5%	55.0%

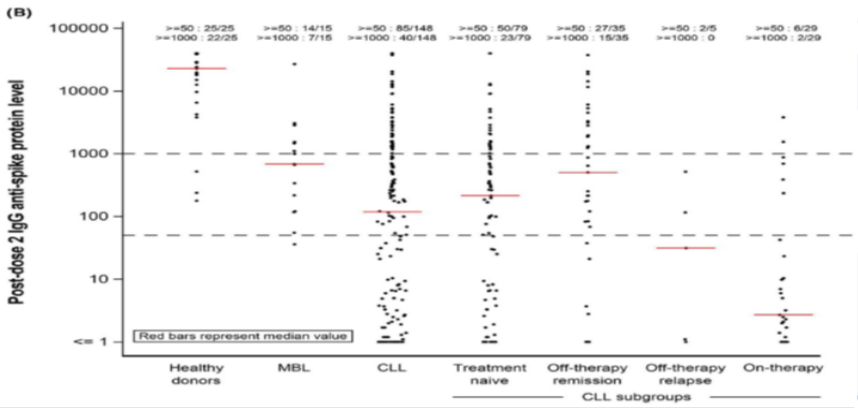
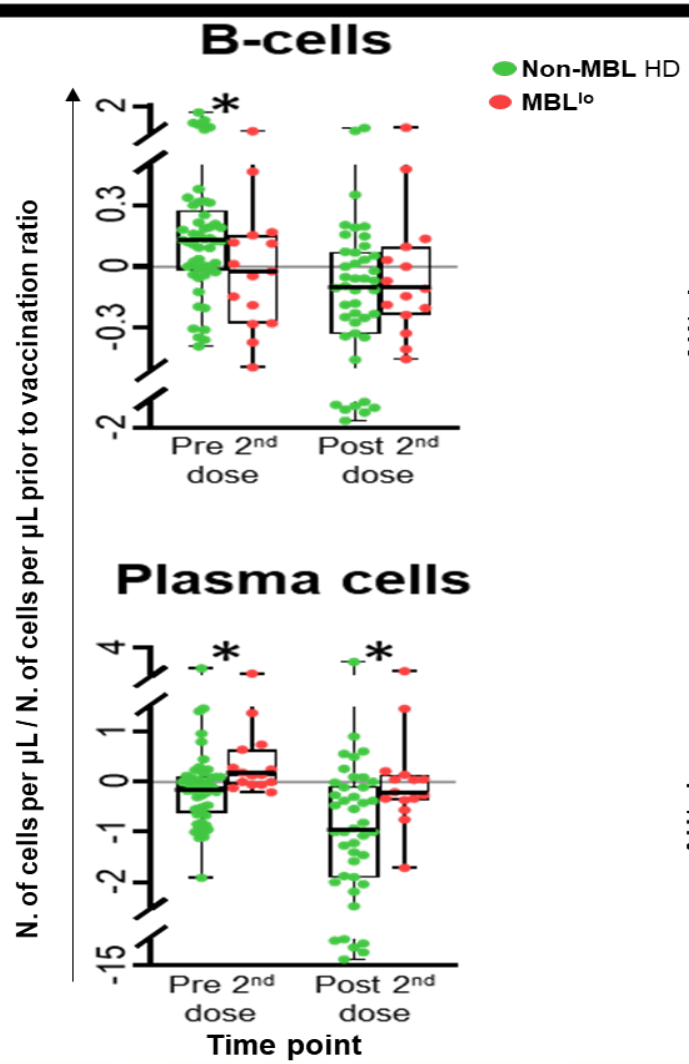


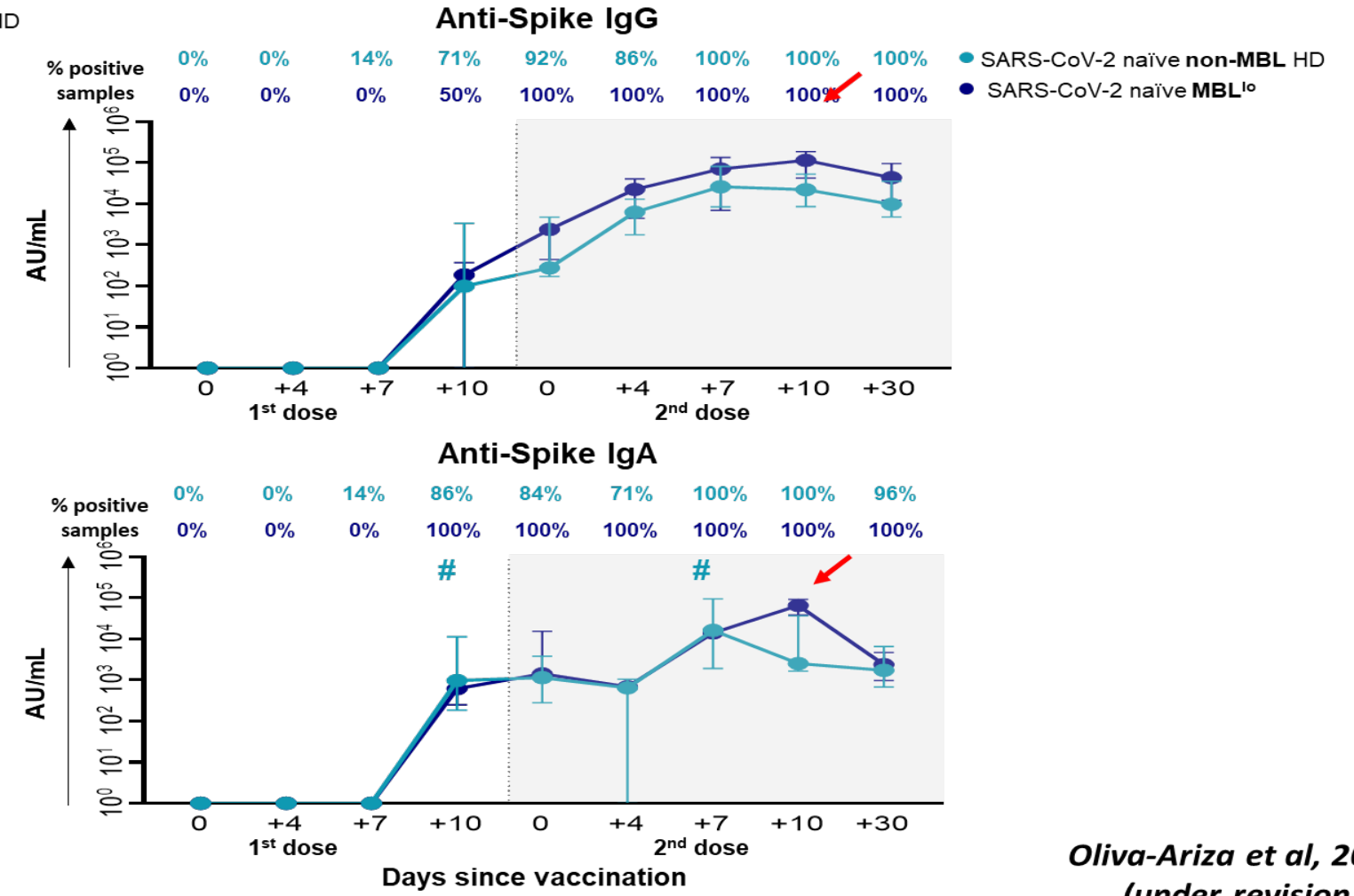
TABLE 4 Multivariate analysis for serologic response in CLL patients

Population	Effect	Adjusted OR	95% CL	*P* value
All CLL patients	Pre-vaccination IgM Reduced *versus* normal/high	9.310	2.871–30.195	0.0002
	On treatment *versus* treatment-naïve/not on treatment	13.091	3.420–50.104	0.0002
CLL (No IgG treatment)	Pre-vaccination IgG2 Reduced *versus* normal/high	1.190	0.512–2.767	0.6858
	Pre-vaccination IgG3 Reduced *versus* normal/high	2.105	0.802–5.530	0.1308

**BTKi treated CLL vs MBL/untreated CLL; Whitaker et al, Vaccine 2021, 1122-30; Muchtar et al, Am J Hematol, 2021, 97: 90-8; Shen et al, Br J Haematol, 2021*

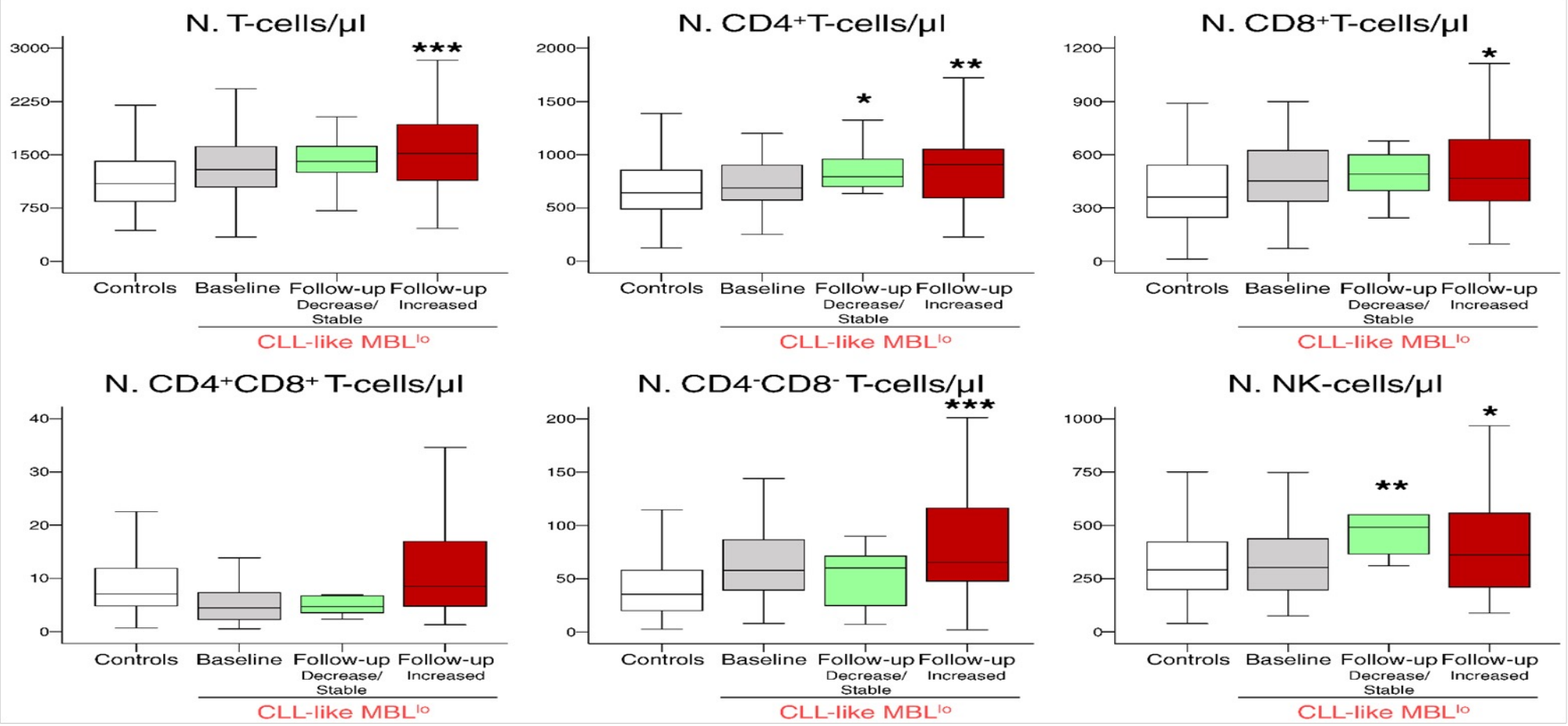
Humoral immune response to SARS-CoV-2 vaccination in COVID-19 naïve MBL^{lo} subjects





Oliva-Ariza et al, 2023 (under revision)

Altered T- and NK- cell counts in MBL^{lo} cases with increased clone size in PB



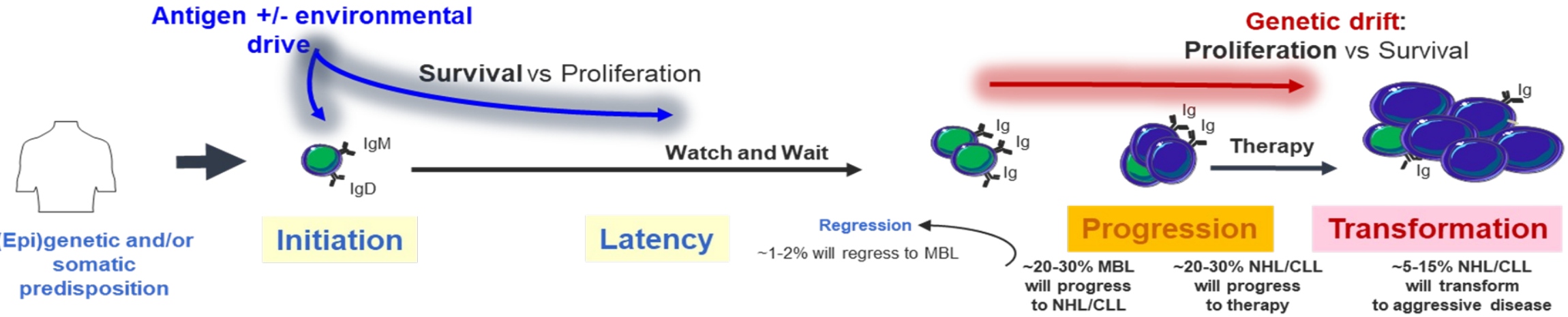
Increase in PB counts of T and NK cells in CLL-like MBL^{lo} subjects parallel to changes in clone size

**P-value* <0.05, ** *P-value* <0.01, ****P-value* ≤0.001 vs. Controls

Criado et al, Leukemia 2108

Natural history of MBL is affected by environmental (antigen) and intrinsic (immune) factors

Normal B cells → Oligoclonal MBL^{lo} → Monoclonal MBL^{lo} → Monoclonal MBL^{lo} (>genetic alterations) → MBL^{hi} → Leukemia NHL → Aggressive Leukemia NHL



↓ B cell production → ↓ B cell repertoire → Selective antibody deficiency → Immunosenescence

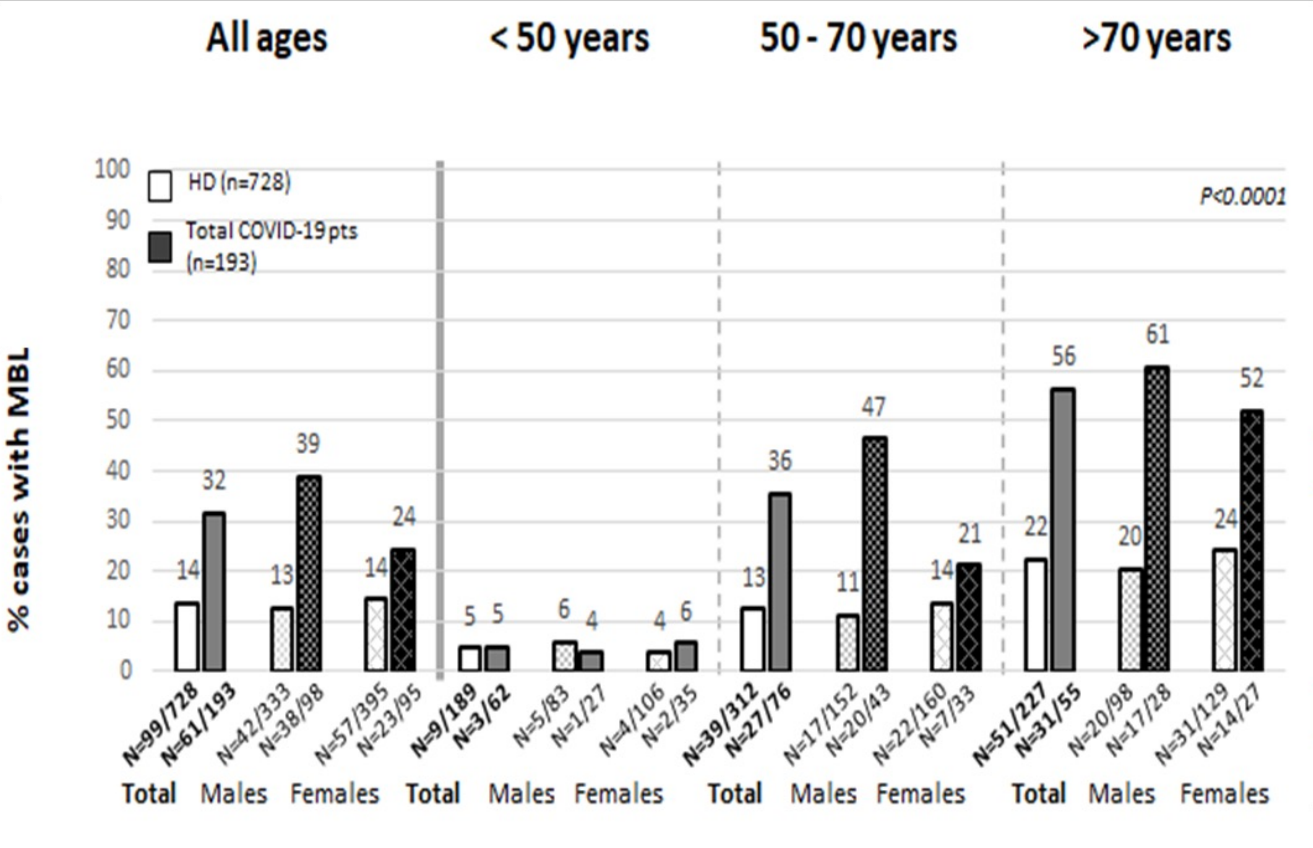
Increased numbers of dysfunctional T and NK cells

Severe infections + second neoplasias / premature deaths (2/1000 per year)

MBL ~3-14% of adults (>40y) ⟶ 509.590 NHL/CLL in 2018

Slide prepared by Francesco Forconi

PREVALENCE OF MBL^{lo} IN (HOSPITALIZED) COVID-19 PATIENTS vs THE GENERAL POPULATION

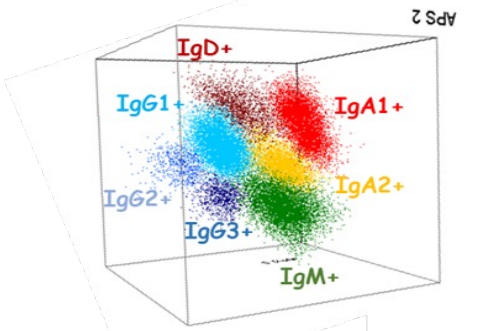


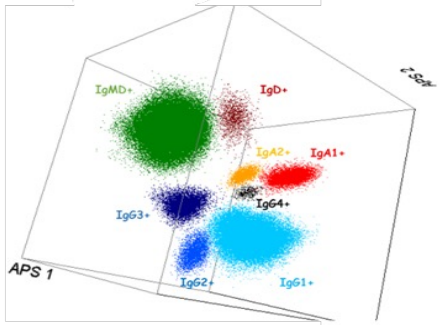
Prediction of mild vs severe COVID-19

Variables	Univariate analysis			Multivariate analysis	
	Non-hospitalized	Hospitalized	P-value	OR (95%CI)	P-value
Sex (male)	42/114 (37%)	91/135 (67%)	<0.0001	2.83 (1.29 – 6.21)	0.01
Dyspnea	36/107 (33%)	95/134 (71%)	<0.0001	4.88 (2.17 – 10.93)	<0.0001
Fever	56/114 (49%)	104/135 (77%)	<0.0001	3.71 (1.52 – 9.06)	0.004
Presence of MBL^{lo}	18/114 (16%)	53/135 (39%)	<0.0001	2.97 (1.19 – 7.42)	0.02
Anti-SARS-CoV-2 IgA ≥24 AU/mL	61/114 (54%)	112/134 (84%)	<0.0001	5.36 (2.13 – 13.52)	<0.0001
Eosinophils <20/µL	17/114 (15%)	71/135 (53%)	<0.0001	6.16 (2.37 – 16.04)	<0.0001
Neutrophils >6000/µL	14/114 (12%)	55/135 (41%)	<0.0001	4.09 (1.48 – 11.3)	0.007
B-cells <100/µL	18/114 (16%)	63/135 (47%)	<0.0001	3.6 (1.3 – 9.99)	0.01
NK cells <150/µL	32/114 (28%)	54/135 (40%)	0.05	3.14 (1.21 – 8.13)	0.02

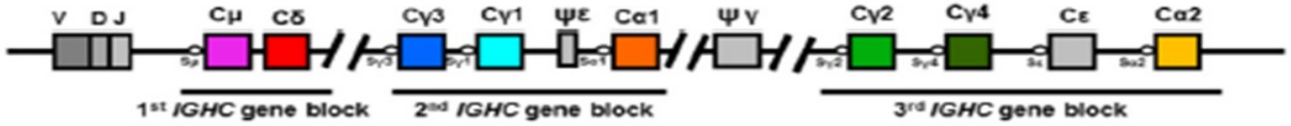
Oliva-Ariza et al, Blood 2022

Distribution of normal PB B-cell and plasma cell subsets through life

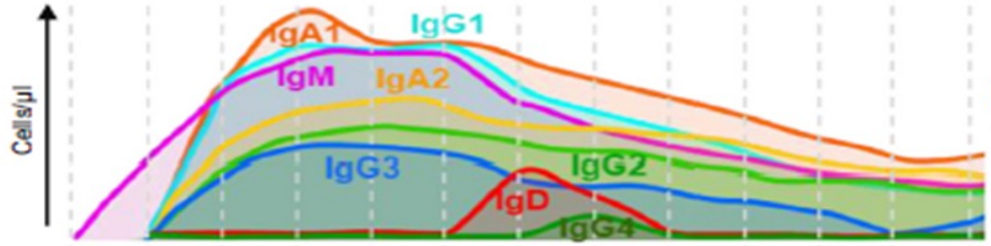




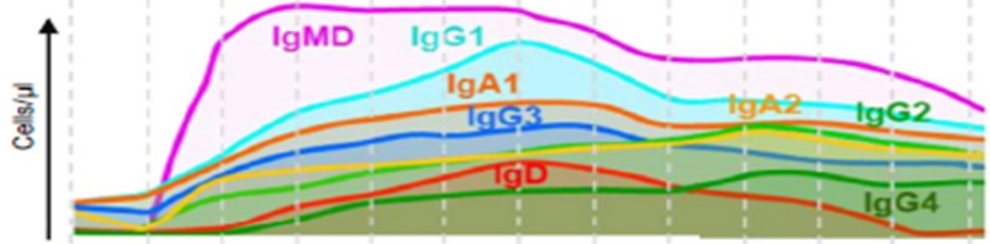
Age-related patterns for plasma cells, memory B-cells, and Ig levels



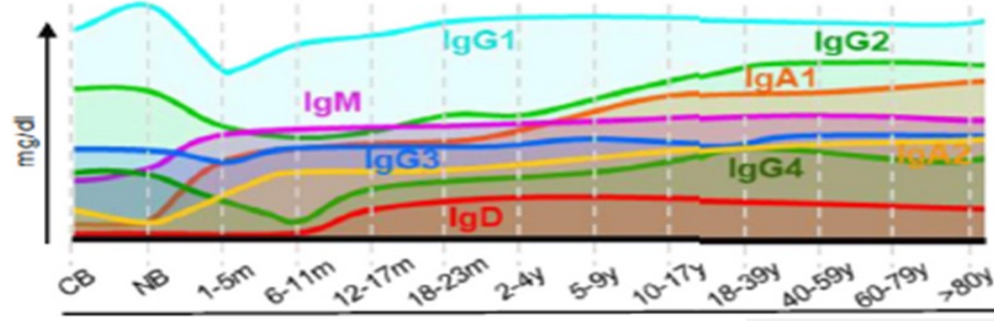
Plasma cells



Memory B- cells



Soluble Ig levels



Real-time (ongoing) B-cell responses

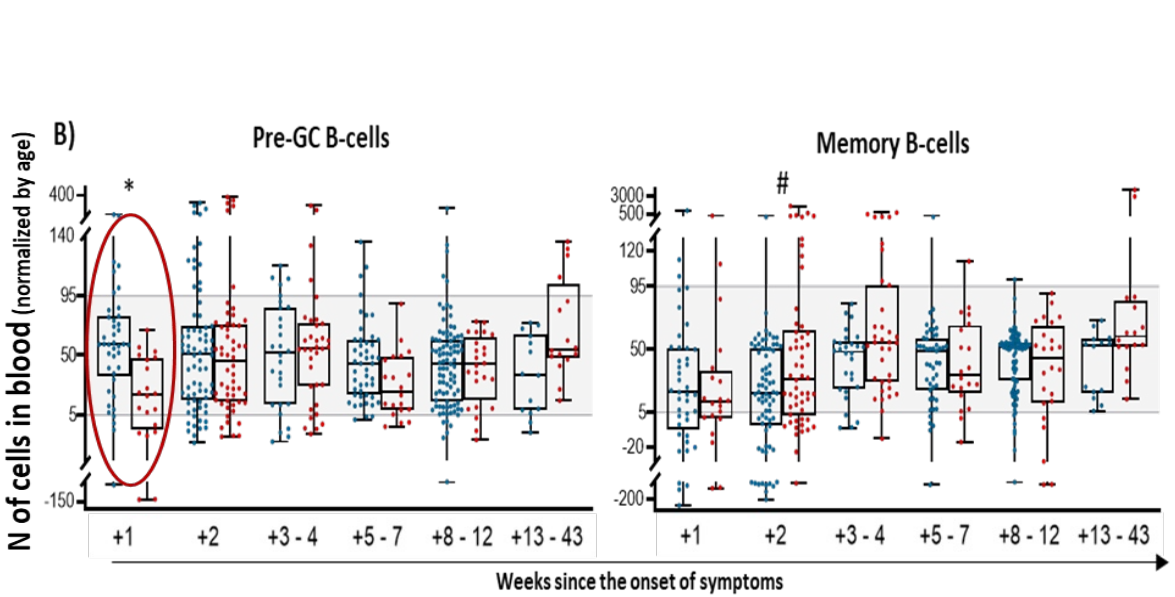
Long-term humoral immunity

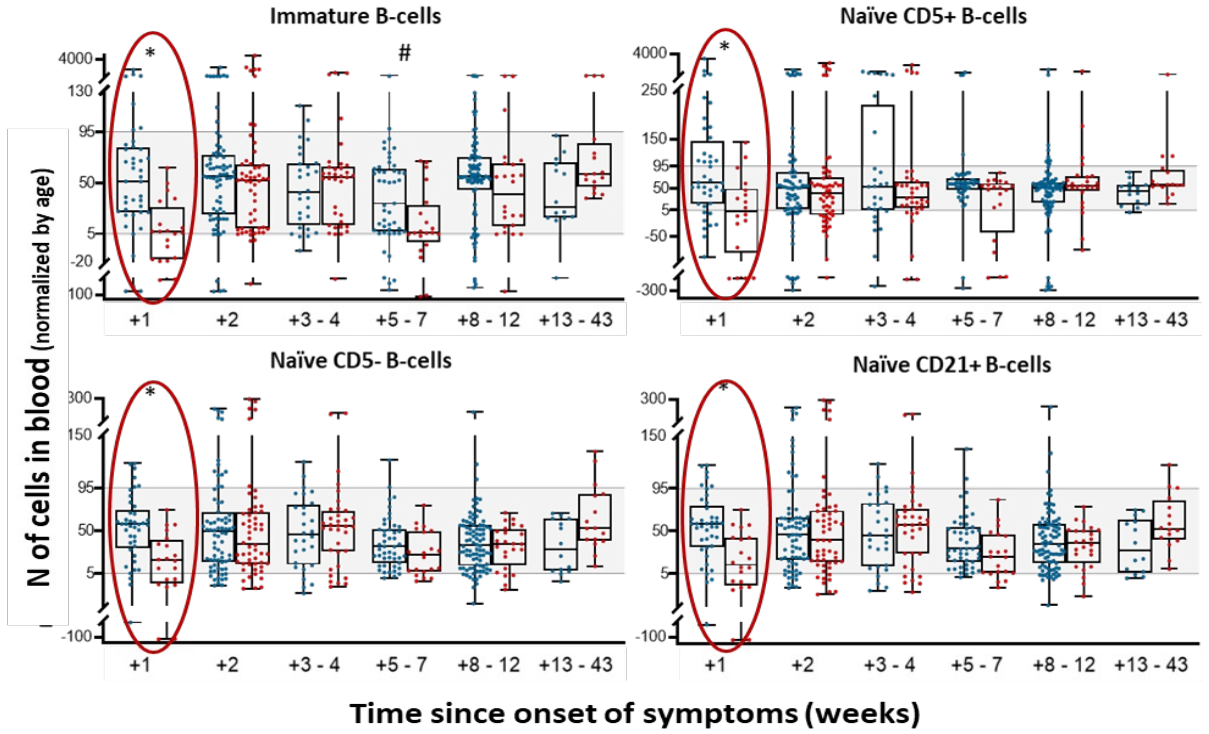
Short-term humoral immunity

y: years
m: months
Ig: immunoglobulin
IGHC: immunoglobulin heavy chain constant region

Blanco et al, J Allergy Clin Immunol 2018

PRE-GERMINAL CENTER B-CELLS IN BLOOD OF MBL^{lo} VS NON-MBL PATIENTS DURING AND AFTER COVID-19





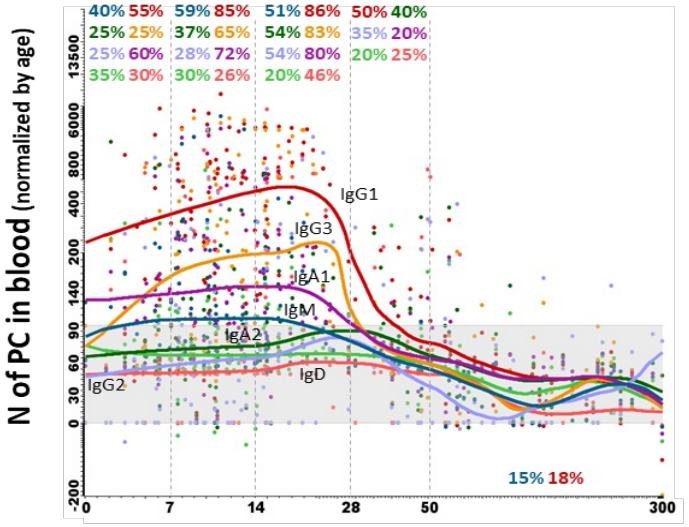
Delayed plasma cell peak in blood of MBL^{lo} vs non-MBL patients during COVID-19 is associated with decreased pre-germinal center B cell counts

ECRIN M3
Early Cancer Research Initiative Network

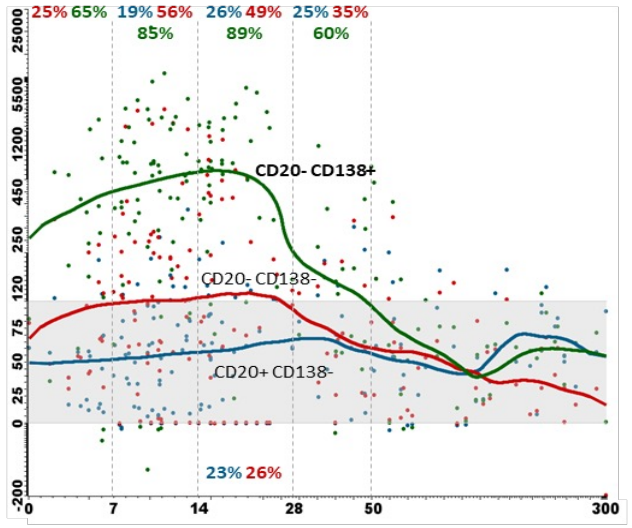
Oliva-Ariza et al, Am J Hematol, 2023

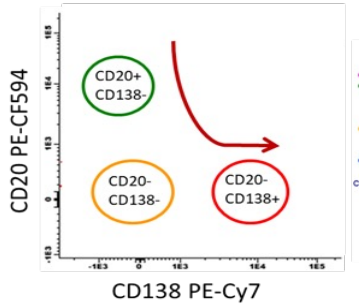
PLASMA CELL KINETICS IN BLOOD OF MBL^{lo} VS NON-MBL PATIENTS DURING AND AFTER COVID-19

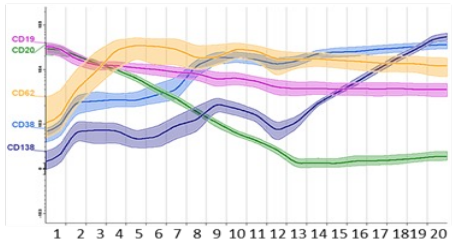
Subsets of plasma cells by IgH subclass

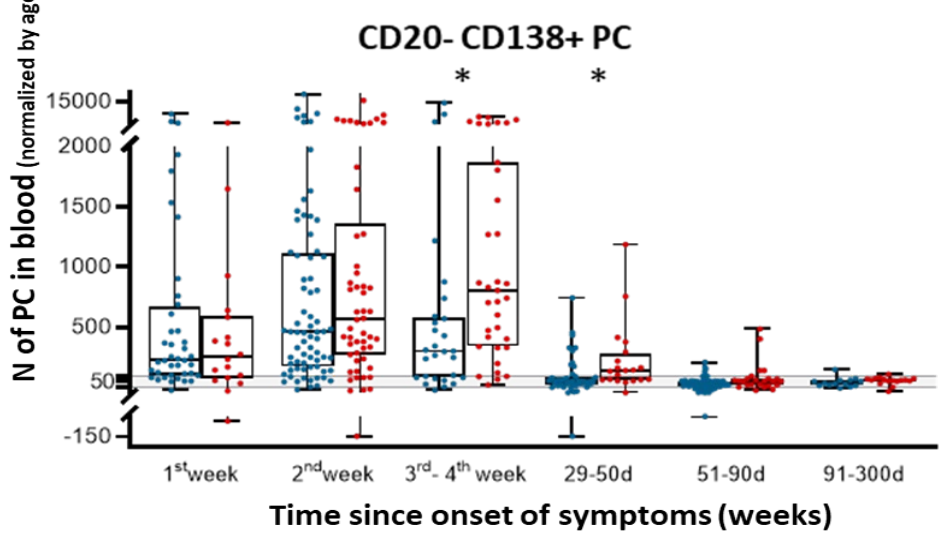


Maturation-associated subsets of plasma cells







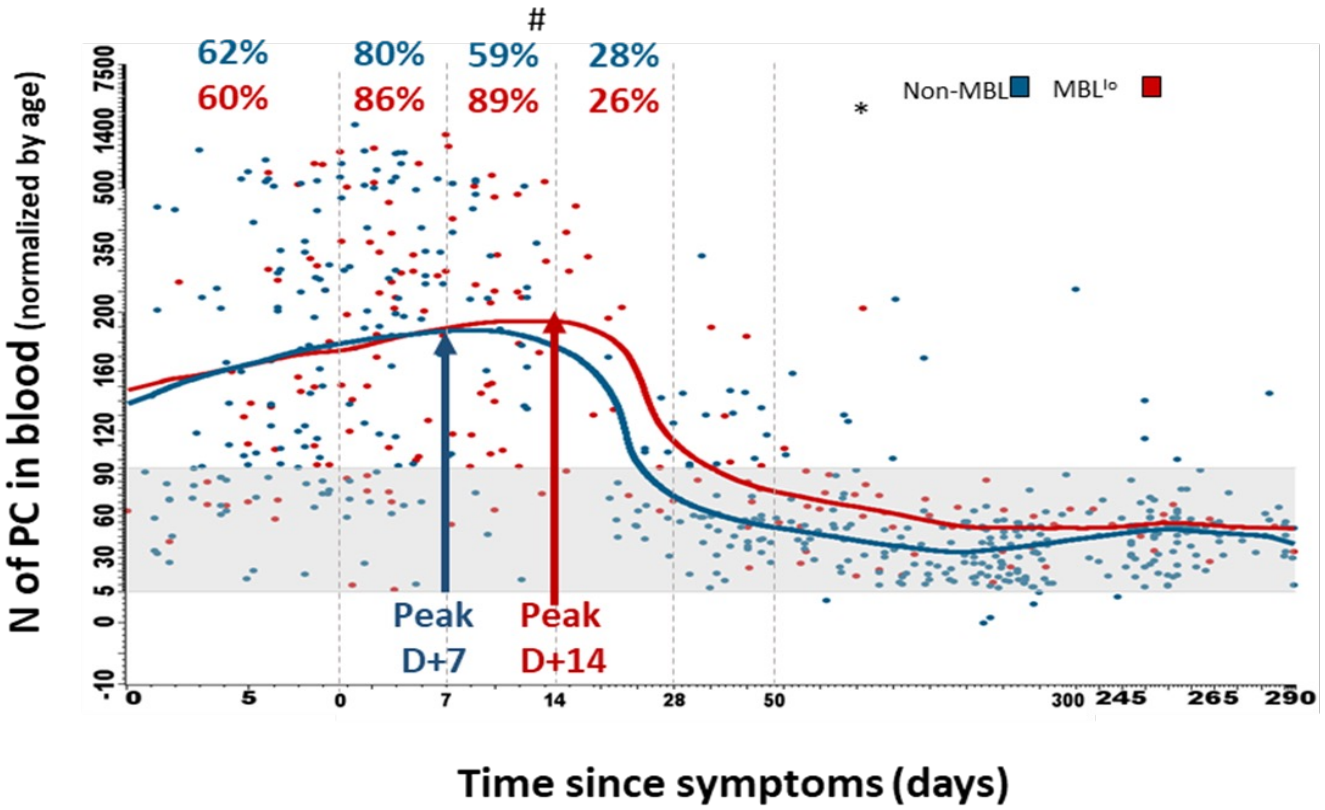


Delayed plasma cell peak in blood of MBL^{lo} vs non-MBL is at the expense of more mature IgG1, IgG3 and IgA1 PC

Oliva-Ariza et al, Am J Hematol, 2023

ECRIN M3 Early Cancer Research Initiative Network

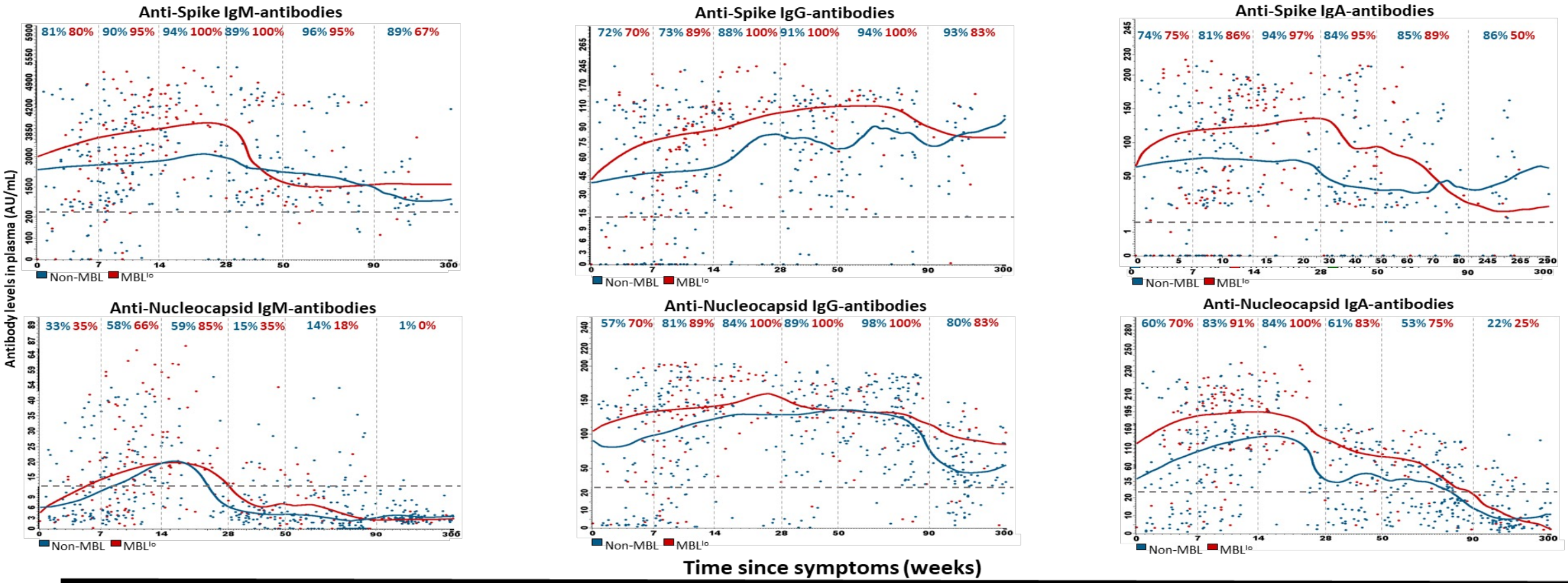
MBL^{lo} vs non-MBL (HOSPITALIZED) COVID-19 PATIENTS: Plasma cell response in blood



Increased frequency of MBL in (more) severe COVID-19 is associated with delayed plasma cell peak in blood during active COVID-19

Oliva-Ariza et al, Blood 2022; Oliva-Ariza et al, Am J Hematol 2023

ANTI-SARS-CoV-2 ANTIBODY LEVELS IN MBL^{lo} VS NON-MBL PATIENTS DURING AND AFTER COVID-19



Delayed plasma cell peak in blood of MBL^{lo} vs non-MBL patients during COVID-19 is associated with decreased pre-germinal center B cell counts

Oliva-Ariza et al, Am J Hematol 2023

Concluding remarks

- The prevalence of MBL^{lo} in the general population is high, increases with age and shows a slight prevalence in men vs women similarly to MBL^{hi} and CLL.

- MBL^{lo} clones persist and frequently increase in size in blood, but with a low rate of progression to MBL^{hi} and CLL in the medium-term (higher among CLL family members than in sporadic cases). However, the small MBL^{lo} clones are not genetically stable and acquire altered profiles similar to MBL^{hi} cases.

- Despite its low rate of leukemia transformation, MBL^{lo} is associated with a significantly greater susceptibility to (more) severe infections and (lymphoid) cancer.

- A strong association between MBL^{lo} and more severe COVID-19 exists, which is associated with decreased numbers of pre-germinal center B cells and a delayed plasma cell peak, but significantly greater (transient) SARS-CoV-2 antibody levels in response to both infection and vaccination.

- The precise the above, the ontogenic pathways and the mechanisms of immune dysregulation in MBL^{lo}, still remain poorly understood.

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